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L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2004-518503/APPS

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L1 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2004:2882 HCAPLUS Full-text  
 DOCUMENT NUMBER: 140:77154  
 TITLE: Preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia  
 INVENTOR(S): Egggenweiler, Hans-Michael; Wolf, Michael  
 PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany  
 SOURCE: PCT Int. Appl., 125 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000839	A1	20031231	WO 2003-EP4434	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10227269	A1	20040108	DE 2002-10227269	20020619
CA 2489902	A1	20031231	CA 2003-2489902	20030428
AU 2003232215	A1	20040106	AU 2003-232215	20030428
BR 2003011879	A	20050315	BR 2003-11879	20030428
EP 1513837	A1	20050316	EP 2003-760583	20030428
EP 1513837	B1	20060830		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1662529	A	20050831	CN 2003-814060	20030428
JP 2005530825	T	20051013	JP 2004-514623	20030428
AT 338041	T	20060915	AT 2003-760583	20030428
US 2005222160	A1	20051006	US 2004-518503	20041220 <--
PRIORITY APPLN. INFO.:			DE 2002-10227269	A 20020619
			WO 2003-EP4434	W 20030428

OTHER SOURCE(S): MARPAT 140:77154

ED Entered STN: 02 Jan 2004

AB Title compds. I [R1, R2 = H, OH, OR8, etc.; R8 = A, cycloalkyl, alkenyl, etc.; R3 = H, A"R7, COA"R7, etc.; A = alkyl, alkenyl; R7 = H, CO2H, CONH2, etc.; A" = alkylene, alkenylene, cycloalkylene, etc.; V, W = O, OH with the proviso that if V = O, then W = H, H; B = (un)substituted aromatic isocyclic, heterocyclic e.g., pyridyl, pyridyl-N-oxide, thienyl, etc.; X = N, CR3] their pharmaceutically acceptable salts and formulations were prepared For example,

coupling of acid chloride II, e.g., prepared from 4-methyl-2-pyridin-2-ylthiazole-5-carboxylic acid Me ester in 3-steps, and 3-(3-cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine afforded claimed thiazole III. Compds. I are claimed useful as phosphodiesterase IV inhibitors (no data provided) for the treatment of osteoporosis, tumors, cachexia, etc.

IC ICM C07D417-14  
ICS C07D417-06; A61K031-50; A61P011-06; A61P019-02; A61P019-10;  
A61P029-00; A61P035-00

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1, 63

ST osteoporosis prepn phosphodiesterase thiazole inhibition; tumor prepn  
phosphodiesterase thiazole inhibition; cachexia prepn phosphodiesterase  
thiazole inhibition

IT Inflammation  
(Crohn's disease; preparation of thiazoles as phosphodiesterase IV  
inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT Intestine, disease  
(Crohn's; preparation of thiazoles as phosphodiesterase IV inhibitors for  
the treatment of osteoporosis, tumors and cachexia)

IT Dermatitis  
(atopic; preparation of thiazoles as phosphodiesterase IV inhibitors for  
the  
treatment of osteoporosis, tumors and cachexia)

IT Bronchi, disease  
Inflammation  
(chronic bronchitis; preparation of thiazoles as phosphodiesterase IV  
inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT Neoplasm  
(metastasis; preparation of thiazoles as phosphodiesterase IV inhibitors  
for  
the treatment of osteoporosis, tumors and cachexia)

IT AIDS (disease)  
Allergy  
Allergy inhibitors  
Anti-AIDS agents  
Anti-inflammatory agents  
Antiartherosclerotics  
Antiasthmatics  
Antidiabetic agents  
Antirheumatic agents  
Antitumor agents  
Arteriosclerosis  
Asthma  
Autoimmune disease  
Cachexia  
Cardiovascular agents  
Diabetes mellitus  
Heart, disease  
Human  
Inflammation  
Multiple sclerosis  
Neoplasm  
Osteoporosis  
Psoriasis  
Rheumatoid arthritis  
Sepsis  
Skin, disease  
(preparation of thiazoles as phosphodiesterase IV inhibitors for the  
treatment of osteoporosis, tumors and cachexia)

IT Inflammation

## Intestine, disease

(ulcerative colitis; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 640743-35-7P 640743-36-8P 640743-37-9P 640743-38-0P,  
1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-39-1P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-40-4P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-41-5P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-42-6P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-43-7P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-44-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-45-9P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-46-0P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-47-1P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-48-2P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-49-3P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-50-6P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-phenylthiazol-5-yl)methanone 640743-51-7P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-methoxyphenyl)thiazol-5-yl)methanone 640743-52-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-aminophenyl)thiazol-5-yl)methanone 640743-53-9P 640743-54-0P  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of thiazoles as phosphodiesterase IV inhibitors

for the treatment of osteoporosis, tumors and cachexia)

IT 640743-56-2P 640743-57-3P 640743-58-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 9036-21-9, Phosphodiesterase IV

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 109-77-3, Propanedinitrile 937-14-4 257876-11-2 438627-45-3,  
3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-55-1,  
4-Methyl-2-pyridin-2-ylthiazole-5-carboxylic acid methyl ester  
640743-59-5, 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-60-8, 3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-61-9 640743-62-0 640743-63-1 640743-64-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2 1 SEA FILE=WPIX ABB=ON PLU=ON US2004-518503/APPS

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YOU HAVE REQUESTED DATA FROM FILE 'WPIX' - CONTINUE? (Y)/N:y

L2 ANSWER 1 OF 1 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2004-099097 [10] WPIX  
 DOC. NO. CPI: C2004-040948 [10]  
 TITLE: New thienyl or thiazolyl-substituted 3-phenyl-5,6-dihydro-4H-pyridazines, useful as phosphodiesterase IV inhibitors for treating e.g. asthma, allergy, inflammation, or autoimmune or myocardial disease  
 DERWENT CLASS: B02; B03; B05; C02; C03; D21  
 INVENTOR: EGGENWEILER H; EGGGENWEILER H; EGGGENWEILER H M; WOLF M  
 PATENT ASSIGNEE: (EGGE-I) EGGENWEILER H; (MERE-C) MERCK PATENT GMBH; (WOLF-I) WOLF M  
 COUNTRY COUNT: 101

## PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004000839	A1	20031231	(200410)	* DE	125 [0]	
DE 10227269	A1	20040108	(200412)	DE		
AU 2003232215	A1	20040106	(200447)	EN		
EP 1513837	A1	20050316	(200519)	DE		
BR 2003011879	A	20050315	(200522)	PT		
KR 2005019141	A	20050228	(200545)	KO		C07D417-14
US 20050222160	A1	20051006	(200566)	EN		
JP 2005530825	W	20051013	(200568)	JA	73	C07D417-06
MX 2004012428	A1	20050501	(200572)	ES		
CN 1662529	A	20050831	(200621)	ZH	[1]	
ZA 2005000484	A	20060426	(200635)	EN	130	C07D000-00
EP 1513837	B1	20060830	(200657)	DE		
DE 50304867	G	20061012	(200670)	DE		

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004000839	A1	WO 2003-EP4434	20030428
DE 10227269	A1	DE 2002-10227269	20020619
AU 2003232215	A1	AU 2003-232215	20030428
BR 2003011879	A	BR 2003-11879	20030428
DE 50304867	G	DE 2003-504867	20030428
EP 1513837	A1	EP 2003-760583	20030428
EP 1513837	B1	EP 2003-760583	20030428
DE 50304867	G	EP 2003-760583	20030428
EP 1513837	A1	WO 2003-EP4434	20030428
US 20050222160	A1	WO 2003-EP4434	20030428
JP 2005530825	W	WO 2003-EP4434	20030428
MX 2004012428	A1	WO 2003-EP4434	20030428
EP 1513837	B1	WO 2003-EP4434	20030428
DE 50304867	G	WO 2003-EP4434	20030428
JP 2005530825	W	JP 2004-514623	20030428
MX 2004012428	A1	MX 2004-12428	20041209

KR 2005019141 A  
 US 20050222160 A1  
 ZA 2005000484 A  
 CN 1662529 A  
 CN 1662529 A

KR 2004-720522 20041217  
US 2004-518503 20041220  
 ZA 2005-484 20050118  
 CN 2003-814060 20030428  
 WO 2003-EP4434 20030428

## FILING DETAILS:

PATENT NO	KIND		PATENT NO	
AU 2003232215	A1	Based on	WO 2004000839	A
EP 1513837	A1	Based on	WO 2004000839	A
BR 2003011879	A	Based on	WO 2004000839	A
JP 2005530825	W	Based on	WO 2004000839	A
MX 2004012428	A1	Based on	WO 2004000839	A
EP 1513837	B1	Based on	WO 2004000839	A
DE 50304867	G	Based on	EP 1513837	A
DE 50304867	G	Based on	WO 2004000839	A

PRIORITY APPLN. INFO: DE 2002-10227269 20020619

## INT. PATENT CLASSIF.:

MAIN: C07D; C07D417-06; C07D417-14

SECONDARY: A61K; A61P; A61K031-501; A61P001-00; A61P001-04;  
 A61P001-16; A61P011-00; A61P011-02; A61P011-06;  
 A61P011-08; A61P013-08; A61P013-12; A61P017-00;  
 A61P017-02; A61P017-04; A61P017-06; A61P019-02;  
 A61P019-06; A61P019-10; A61P021-04; A61P025-00;  
 A61P025-14; A61P025-16; A61P025-24; A61P025-28;  
 A61P027-02; A61P027-14; A61P029-00; A61P003-10;  
 A61P031-04; A61P031-10; A61P031-16; A61P031-18;  
 A61P031-20; A61P031-22; A61P033-02; A61P033-06;  
 A61P035-00; A61P037-02; A61P037-06; A61P037-08;  
 A61P043-00; A61P005-14; A61P007-00; A61P007-04;  
 A61P007-06; A61P009-00; A61P009-10

IPC ORIGINAL: A61K0031-50 [I,A]; A61K0031-50 [I,A]; A61K0031-50 [I,C];  
 A61P0011-00 [I,C]; A61P0011-00 [I,C]; A61P0011-06 [I,A];  
 A61P0011-06 [I,A]; A61P0019-00 [I,C]; A61P0019-00 [I,C];  
 A61P0019-02 [I,A]; A61P0019-02 [I,A]; A61P0019-10 [I,A];  
 A61P0019-10 [I,A]; A61P0029-00 [I,A]; A61P0029-00 [I,A];  
 A61P0029-00 [I,C]; A61P0035-00 [I,A]; A61P0035-00 [I,A];  
 A61P0035-00 [I,C]; C07D0417-00 [I,C]; C07D0417-00 [I,C];  
 C07D0417-00 [I,C]; C07D0417-06 [I,A]; C07D0417-06 [I,A];  
 C07D0417-14 [I,A]; C07D0417-14 [I,A]

IPC RECLASSIF.: A61K0031-501 [I,A]; A61K0031-501 [I,C]; A61P0001-00 [I,A]  
 ; A61P0001-00 [I,C]; A61P0001-04 [I,A]; A61P0001-16 [I,A]  
 ; A61P0011-00 [I,A]; A61P0011-00 [I,C]; A61P0011-02 [I,A]  
 ; A61P0011-06 [I,A]; A61P0011-08 [I,A]; A61P0013-00 [I,C]  
 ; A61P0013-08 [I,A]; A61P0013-12 [I,A]; A61P0017-00 [I,A]  
 ; A61P0017-00 [I,C]; A61P0017-02 [I,A]; A61P0017-04 [I,A]  
 ; A61P0017-06 [I,A]; A61P0019-00 [I,C]; A61P0019-02 [I,A]  
 ; A61P0019-06 [I,A]; A61P0019-10 [I,A]; A61P0021-00 [I,C]  
 ; A61P0021-04 [I,A]; A61P0025-00 [I,A]; A61P0025-00 [I,C]  
 ; A61P0025-14 [I,A]; A61P0025-16 [I,A]; A61P0025-24 [I,A]  
 ; A61P0025-28 [I,A]; A61P0027-00 [I,C]; A61P0027-02 [I,A]  
 ; A61P0027-14 [I,A]; A61P0029-00 [I,A]; A61P0029-00 [I,C]  
 ; A61P0003-00 [I,C]; A61P0003-10 [I,A]; A61P0031-00 [I,C]  
 ; A61P0031-04 [I,A]; A61P0031-10 [I,A]; A61P0031-16 [I,A]  
 ; A61P0031-18 [I,A]; A61P0031-20 [I,A]; A61P0031-22 [I,A]  
 ; A61P0033-00 [I,C]; A61P0033-02 [I,A]; A61P0033-06 [I,A]  
 ; A61P0035-00 [I,A]; A61P0035-00 [I,C]; A61P0037-00 [I,C]

; A61P0037-02 [I,A]; A61P0037-06 [I,A]; A61P0037-08 [I,A]  
 ; A61P0043-00 [I,A]; A61P0043-00 [I,C]; A61P0005-00 [I,C]  
 ; A61P0005-14 [I,A]; A61P0007-00 [I,A]; A61P0007-00 [I,C]  
 ; A61P0007-04 [I,A]; A61P0007-06 [I,A]; A61P0009-00 [I,A]  
 ; A61P0009-00 [I,C]; A61P0009-10 [I,A]; C07D0417-00 [I,C]  
 ; C07D0417-06 [I,A]; C07D0417-14 [I,A]; A61K0031-50 [I,A]  
 ; A61K0031-50 [I,C]

## BASIC ABSTRACT:

WO 2004000839 A1 UPAB: 20060121

NOVELTY - 1-((2-(Hetero)aryl-5-thienyl or -thiazolyl)-alkyl or -carbonyl)-3-phenyl-5,6-dihydro-4H-pyridazine derivatives (I) are new.

DETAILED DESCRIPTION - Pyridazine derivatives of formula (I) and their derivatives, solvates and stereoisomers (including mixtures in all ratios) are new.

R1, R2 = H, OH, OR8, SR8, SOR8, SO2R8 or halo;  
 R1 + R2 = OCH2O or OCH2CH2O;  
 R3 = H, A2R7, COA2R7, COOA2R7, CONH2, CONHA2R7, CON(A2R7)A3R7, NH2, NHA2R7, N(A2R7)A3R7, NHCOA2R7 or NHCOOA2R7;  
 one of V, W' = O and the other = H2;  
 B = isocyclic or heterocyclic aromatic group, substituted by R4-R6;  
 X = N or C(R31);  
 R31 = R3;  
 R4-R6 = H, A2R7, OH, OA2R7, NO2, NH2, NHA2R7, N(A2R7)A3R7, NHCOA2R7, NHCOOA2R7, NHCONH2, NHCONHA2R7, NHCON(A2R7)A3R7, halo, COOH, COOA2R7, CONH2, CONHA2R7, CON(A2R7)A3R7, -NH-N=C(CN)-Q or lactam group of formula (a);  
 Q = CN, CONH2 or tetrazol-5-yl;  
 R7 = H, COOH, COOA, CONH2, CONHA, CONAA1, NH2, NHA, NAA1, NHCOA, NHCOOA, OH or OA;  
 R8 = A, 3-7C cycloalkyl, 4-8C alkylencycloalkyl or 2-8C alkenyl;  
 R9 = 1-10C alkyl, 3-7C cycloalkyl, 4-8C alkylencycloalkyl or 2-8C alkenyl (all optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH, NMe, NET and/or CH=CH; and optionally substituted (os) by 1-7 F and/or Cl and/or by R7);  
 Y' = 1-10C alkylene or 2-8C alkenylene (both optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH or NR10; and os by 1-7 F and/or Cl);  
 A, A1 = 1-10C alkyl or 2-8C alkenyl (both optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH or NR10; and os by 1-7 F and/or Cl); or Ar or Het;  
 A + A1 = 2-7C alkylene (optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH or NR9);  
 A2, A3 = direct bond; or 1-10C alkylene, 2-8C alkenylene or 3-7C cycloalkylene (all optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH or NR9; and os by 1-7 F and/or Cl);  
 A2+A3 = 2-7C alkylene (optionally having 1-3 CH2 replaced by O, S, SO, SO2, NH, NR9, NHCOR9 or NHCOOR9);  
 Ar = phenyl, naphthyl, fluorenyl or biphenyl (all os by 1-3 of halo, R11, OR10, N(R10)2, NO2, CN, COOR10, CON(R10)2, NR10COR10, NR10CON(R10)2, NR10SO2A, COR10, SO2N(R10)2 or S(O)mR11);  
 R10 = H or 1-6C alkyl;  
 R11 = 1-6C alkyl;  
 Het = mono- or bicyclic, saturated, unsaturated or aromatic heterocycle containing 1 or 2 of N, O and/or S (os by 1 or 2 of =O, halo, R11, OR10, N(R10)2, NO2, CN, COOR10, CON(R10)2, NR10COR10, NR10CON(R10)2, NR10SO2R11, COR10, SO2N(R10)2 or S(O)mR11);  
 m = 0-2;  
 n = 0-4.  
 An INDEPENDENT CLAIM is also included for the preparation of (I).  
 ACTIVITY - Antiasthmatic; Antiallergic; Antiinflammatory; Dermatological; Antipsoriatic; Immunosuppressive; Antirheumatic; Antiarthritic; Neuroprotective; Antidiabetic; Antiulcer; Osteopathic;

Immunomodulator; Cytostatic; Antibacterial; Nootropic; Antiarteriosclerotic; Anti-HIV; Cardiant; Vasotropic; Antigout; Analgesic; Antipyretic; Ophthalmological; Antianemic; Hepatotropic; Nephrotropic; Hypotensive; Antidepressant; Antiparkinsonian; Antiaddictive; Virucide; Fungicide.

MECHANISM OF ACTION - Phosphodiesterase IV (PDE IV) Inhibitor.

USE - (I) Are PDE IV inhibitors, used for treating diseases involving PDE IV-mediated regulation of the activation and degranulation of eosinophils, specifically asthma, allergy, chronic bronchitis, atopic dermatitis, psoriasis, other skin diseases, inflammatory diseases, autoimmune diseases (e.g. rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes or ulcerative colitis), osteoporosis, transplant rejection reactions, cachexia, tumor growth or metastasis, sepsis, memory disorders, atherosclerosis, AIDS, myocardial diseases (specifically of inflammatory and immunological type), coronary heart disease, (ir)reversible myocardial ischemia/reperfusion damage, acute or chronic heart failure or restenosis (including in-stent or stent-in-stent restenosis) (all claimed). Numerous more specific diseases to be treated are specified in the claims, e.g.: several specific types of asthma, bronchitis, bronchiectasis and other obstructive/inflammatory respiratory disorders (e.g. emphysema, dust in the lungs, chronic eosinophilic pneumonia, allergic obstructive pulmonary disease or broncho-pneumonic aspergillosis); allergic rhinitis, sinusitis, allergic dermatitis, allergic or atopic eczema, nettle rash or urticaria; various types of rheumatoid arthritis (e.g. acute gout arthritis, osteoarthritis, psoriatic arthritis or spondylarthritis); gout; pain or fever associated with inflammation; various types of conjunctivitis or uveitis; several types of autoimmune disease (e.g. hemolytic or aplastic anemia, systemic lupus erythematosus, chronic-active hepatitis, myasthenia gravis, alveolitis, primary biliary cirrhosis, type I diabetes mellitus, keratoconjunctivitis sicca, glomerulonephritis, dandruff or pemphigus); irritable bowel disease; liver damage; pulmonary hypertension; CNS disorders (specifically depression, Parkinson's disease, learning or memory deficiency, tardive dyskinesia, drug addiction or various types of dementia); and TNF-alpha-associated viral, yeast or fungal infections (e.g. HIV-1, HIV-2, HIV-3, cytomegalovirus, influenza virus or herpes virus infections); or chronic lymphocytic leukemia.

ADVANTAGE - (I) Are selective and well tolerated PDE IV inhibitors.

# MANUAL CODE:

CPI: B04-A06; B04-H06B; B04-L05C; B06-A01; B06-D09;  
B06-D18; B07-A01; B07-B01; B07-D10; B07-F01; B10-D03;  
B14-A01; B14-A02; B14-A04; B14-C01; B14-C02; B14-C03;  
B14-C04; B14-C09; B14-D07A; B14-E10C; B14-E11; B14-F01;  
B14-F03; B14-F05; B14-F07; B14-G01B; B14-G02A; B14-G02C;  
B14-G02D; B14-H01; B14-J01; B14-J05; B14-K01; B14-M01C;  
B14-N01; B14-N02; B14-N03; B14-N04; B14-N10; B14-N12;  
B14-N16; B14-N17; B14-R02; B14-S01; B14-S04; C04-A06;  
C04-H06B; C04-L05C; C06-A01; C06-D09; C06-D18; C07-A01;  
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C14-A04; C14-C01; C14-C02; C14-C03; C14-C04; C14-C09;  
C14-D07A; C14-E10C; C14-E11; C14-F01; C14-F03; C14-F05;  
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C14-N03; C14-N04; C14-N10; C14-N12; C14-N16; C14-N17;  
C14-R02; C14-S01; C14-S04; D08-B03

AN 2004-099097 [10] WPIX

DC B02; B03; B05; C02; C03; D21

IC ICM C07D; C07D417-06; C07D417-14

ICS A61K; A61P; A61K031-501; A61P001-00; A61P001-04; A61P001-16;  
A61P011-00; A61P011-02; A61P011-06; A61P011-08; A61P013-08;  
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A61P019-02; A61P019-06; A61P019-10; A61P021-04; A61P025-00;  
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A61P027-14; A61P029-00; A61P003-10; A61P031-04; A61P031-10;

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MC CPI: B04-A06; B04-H06B; B04-L05C; B06-A01; B06-D09; B06-D18; B07-A01;  
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 C14-S04; D08-B03

CMC UPB 20060121

DRN: 0163-U 0180-U 1218-U

DCR: 60080-U 6284-U 86977-U

M1 \*23\* M423 M431 M782 Q233 M905

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DCR: 104225-K 104225-M

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DCN: RA07EZ-K RA07EZ-M

DCR: 122552-K 122552-M

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 M540 M710 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241 P411  
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 M2 \*04\* F011 F012 F013 F014 F015 F530 F710 G013 G015 G100 H2 H211 H5  
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 DCN: RACVZI-M RACVZI-N RACVZI-P RACVZI-T  
 DCR: 835714-M 835714-N 835714-P 835714-T  
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 P423 P431 P433 P434 P446 P451 P510 P517 P520 P522 P526 P616 P625  
 P631 P632 P633 P646 P714 P721 P722 P723 P738 P811 P812 P814 P816  
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 DCR: 835713-M 835713-N 835713-P 835713-T  
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 DCN: RACVZG-M RACVZG-N RACVZG-P RACVZG-T  
 DCR: 835712-M 835712-N 835712-P 835712-T  
 M2 \*08\* F011 F012 F013 F014 F015 F019 F211 F530 F710 G015 G100 H2 H211

H5 H542 H8 J0 J011 J3 J311 M1 M113 M116 M210 M211 M212 M240 M272  
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 DCR: 835710-M 835710-N 835710-P 835710-T  
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 DCR: 835709-M 835709-N 835709-P 835709-T  
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M2 \*16\* F011 F012 F013 F014 F015 F019 F431 F530 F710 G015 G100 H2 H211  
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 P633 P646 P714 P721 P722 P723 P738 P811 P812 P814 P816 P820 P822  
 P921 P922 P924 P943 Q233 M905 M904  
 DCN: RACVZ6-M RACVZ6-N RACVZ6-P RACVZ6-T  
 DCR: 835702-M 835702-N 835702-P 835702-T

M2 \*18\* F011 F012 F013 F014 F015 F019 F431 F530 F710 G015 G100 H2 H211  
 H5 H542 H8 J0 J011 J3 J311 K0 K7 K742 M1 M113 M116 M210 M211  
 M212 M240 M272 M281 M282 M320 M413 M431 M510 M523 M531 M540 M710  
 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241 P411 P420 P421  
 P422 P423 P431 P433 P434 P446 P451 P510 P517 P520 P522 P526 P616  
 P625 P631 P632 P633 P646 P714 P721 P722 P723 P738 P811 P812 P814  
 P816 P820 P822 P921 P922 P924 P943 Q233 M905 M904  
 DCN: RACVZ5-M RACVZ5-N RACVZ5-P RACVZ5-T  
 DCR: 835701-M 835701-N 835701-P 835701-T

M2 \*19\* F011 F012 F013 F014 F015 F019 F431 F530 F710 G015 G100 H2 H211  
 H5 H542 H8 J0 J011 J3 J311 K0 K7 K742 M1 M113 M116 M210 M211  
 M213 M232 M240 M272 M281 M282 M320 M413 M431 M510 M523 M531 M540  
 M710 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241 P411 P420  
 P421 P422 P423 P431 P433 P434 P446 P451 P510 P517 P520 P522 P526  
 P616 P625 P631 P632 P633 P646 P714 P721 P722 P723 P738 P811 P812  
 P814 P816 P820 P822 P921 P922 P924 P943 Q233 M905 M904  
 DCN: RACVZ4-M RACVZ4-N RACVZ4-P RACVZ4-T  
 DCR: 835700-M 835700-N 835700-P 835700-T

M2 \*20\* F011 F012 F013 F014 F015 F019 F431 F530 F710 G015 G030 G111 G553  
 H2 H211 H5 H542 H8 J0 J011 J3 J311 K0 K7 K742 M1 M113 M116 M123  
 M141 M210 M211 M240 M272 M281 M320 M413 M431 M510 M523 M531 M541  
 M710 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241 P411 P420  
 P421 P422 P423 P431 P433 P434 P446 P451 P510 P517 P520 P522 P526  
 P616 P625 P631 P632 P633 P646 P714 P721 P722 P723 P738 P811 P812  
 P814 P816 P820 P822 P921 P922 P924 P943 Q233 M905 M904  
 DCN: RACVZ3-M RACVZ3-N RACVZ3-P RACVZ3-T  
 DCR: 835699-M 835699-N 835699-P 835699-T

M2 \*21\* C216 C316 D010 D019 D020 D021 D022 D029 D040 D049 D140 D150 F010  
 F011 F012 F013 F015 F016 F019 F020 F021 F029 F211 F212 F410 F499  
 F530 F570 F599 F710 G001 G002 G003 G010 G011 G012 G013 G014 G015  
 G016 G019 G020 G021 G022 G029 G030 G031 G039 G040 G050 G100 G111

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G112 G113 G221 G299 G310 G399 G553 G563 H100 H101 H102 H103 H121  
H122 H123 H141 H142 H143 H161 H162 H163 H181 H182 H183 H2 H211  
H212 H213 H321 H322 H323 H341 H342 H343 H361 H362 H363 H401 H402  
H403 H404 H405 H421 H422 H423 H424 H441 H442 H443 H444 H461 H462  
H463 H464 H481 H482 H483 H484 H521 H522 H523 H541 H542 H543 H561  
H562 H563 H581 H582 H583 H594 H599 H600 H608 H609 H621 H622 H623  
H641 H642 H643 H661 H662 H663 H713 H715 H716 H721 H722 H723 J011  
J012 J013 J014 J111 J112 J113 J131 J132 J133 J151 J152 J153 J171  
J172 J173 J211 J212 J221 J222 J231 J232 J241 J242 J251 J252 J261  
J262 J271 J272 J273 J311 J312 J321 J322 J331 J332 J341 J342 J351  
J352 J361 J362 J371 J372 J373 J411 J5 J521 J522 J523 J581 K442  
K499 K620 K630 K640 K699 K810 K820 K830 K850 K899 K910 K920 K999  
L141 L199 L410 L431 L432 L462 L463 L472 L499 L532 L541 L560 L599  
L640 L660 L699 L9 L941 L999 M1 M111 M113 M115 M116 M119 M123  
M125 M126 M129 M131 M135 M136 M137 M139 M141 M142 M143 M146 M147  
M149 M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224  
M225 M226 M231 M232 M233 M240 M262 M271 M272 M273 M280 M281 M282  
M283 M311 M312 M313 M314 M315 M316 M321 M322 M323 M331 M332 M333  
M340 M342 M349 M372 M373 M381 M382 M383 M391 M392 M393 M412 M413  
M431 M510 M511 M512 M513 M522 M523 M530 M531 M532 M533 M540 M541  
M542 M543 M710 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241  
P411 P420 P421 P422 P423 P431 P433 P434 P446 P451 P510 P517 P520  
P522 P526 P616 P625 P631 P632 P633 P646 P714 P721 P722 P723 P738  
P811 P812 P814 P816 P820 P822 P921 P922 P924 P943 Q233 M905  
M904

RIN: 00061 01662

MCN: 0119-00002-M 0119-00002-N 0119-00002-P 0119-00002-T

M2 \*22\*

C216 C316 D010 D019 D020 D021 D022 D029 D040 D049 D140 D150 F010  
F011 F012 F013 F015 F019 F020 F021 F029 F211 F212 F410 F499 F530  
F570 F599 F710 G001 G002 G003 G010 G011 G012 G013 G014 G015 G016  
G019 G020 G021 G022 G029 G030 G031 G039 G040 G050 G100 G111 G112  
G113 G221 G299 G310 G399 G553 G563 H100 H101 H102 H103 H121 H122  
H123 H141 H142 H143 H161 H162 H163 H181 H182 H183 H2 H211 H212  
H213 H321 H322 H323 H341 H342 H343 H361 H362 H363 H401 H402 H403  
H404 H405 H421 H422 H423 H424 H441 H442 H443 H444 H461 H462 H463  
H464 H481 H482 H483 H484 H521 H522 H523 H541 H542 H543 H561 H562  
H563 H581 H582 H583 H594 H599 H600 H608 H609 H621 H622 H623 H641  
H642 H643 H661 H662 H663 H713 H715 H716 H721 H722 H723 J0 J011  
J012 J013 J014 J111 J112 J113 J131 J132 J133 J151 J152 J153 J171  
J172 J173 J211 J212 J221 J222 J231 J232 J241 J242 J251 J252 J261  
J262 J271 J272 J273 J3 J311 J312 J321 J322 J331 J332 J341 J342  
J351 J352 J361 J362 J371 J372 J373 J411 J521 J522 J523 J581 K442  
K499 K620 K630 K640 K699 K810 K820 K830 K850 K899 K910 K920 K999  
L141 L199 L410 L431 L432 L462 L463 L472 L499 L532 L541 L560 L599  
L640 L660 L699 L941 L999 M1 M111 M113 M115 M116 M119 M123 M125  
M126 M129 M131 M135 M136 M137 M139 M141 M142 M143 M146 M147 M149  
M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225  
M226 M231 M232 M233 M240 M262 M271 M272 M273 M280 M281 M282 M283  
M311 M312 M313 M314 M315 M316 M320 M321 M322 M323 M331 M332 M333  
M340 M342 M349 M372 M373 M381 M382 M383 M391 M392 M393 M412 M413  
M431 M510 M511 M512 M513 M522 M523 M530 M531 M532 M533 M540 M541  
M542 M543 M710 M720 M782 N225 N241 N261 N331 N512 P210 P220 P241  
P411 P420 P421 P422 P423 P431 P433 P434 P446 P451 P510 P517 P520  
P522 P526 P616 P625 P631 P632 P633 P646 P714 P721 P722 P723 P738  
P811 P812 P814 P816 P820 P822 P921 P922 P924 P943 Q233 M905  
M904

RIN: 00061 01662

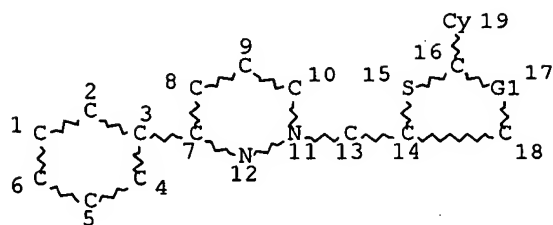
MCN: 0119-00001-M 0119-00001-N 0119-00001-P 0119-00001-T

M2 \*25\*

G015 G100 H4 H401 H441 H5 H541 H7 H721 H8 J0 J011 J3 J371 M210  
M211 M220 M223 M232 M262 M272 M281 M311 M321 M342 M373 M391 M414

M431 M510 M520 M531 M540 M782 Q233 M905 M904  
 DCN: R03442-K R03442-M  
 DCR: 89965-K 89965-M  
 M2 \*26\* D011 D016 D023 D024 D026 D030 E330 E350 H1 H181 H2 H201 H4 H402  
 H421 H461 H5 H541 H8 J0 J013 J2 J211 J251 J261 M1 M116 M210 M211  
 M212 M240 M262 M272 M273 M281 M282 M283 M320 M412 M431 M512 M520  
 M530 M540 M782 M800 Q233 M905 M904  
 RIN: 11065 13275  
 DCN: R04079-K R04079-M R17068-K R17068-M  
 DCR: 110145-K 110145-M  
 M2 \*27\* D011 D920 J5 J521 L9 L941 M280 M320 M412 M431 M511 M520 M530  
 M540 M782 Q233 M905 M904 M910  
 RIN: 01174  
 DCN: R01218-K R01218-M R04867-K R04867-M RA3MZJ-K RA3MZJ-M  
 DCR: 375800-K 375800-M 86977-K 86977-M 86977-U  
 M2 \*28\* D012 D013 D940 G013 G100 H1 H101 H103 H122 H141 J0 J013 J1 J172  
 J3 J331 L9 L910 M210 M211 M273 M281 M311 M313 M321 M332 M342  
 M343 M349 M373 M381 M391 M412 M431 M511 M520 M531 M540 M782 Q233  
 M905 M904 M910  
 DCN: R00180-K R00180-M  
 DCR: 60080-K 60080-M 60080-U  
 M2 \*29\* C316 F012 F013 F014 F112 G010 G013 G100 J5 J521 K0 K4 K442 L9  
 L942 M1 M113 M119 M210 M211 M271 M281 M320 M413 M431 M510 M521  
 M532 M540 M782 Q233 M905 M904  
 DCN: RA027J-K RA027J-M RA06CV-K RA06CV-M  
 DCR: 129270-K 129270-M 208737-K 208737-M  
 M2 \*30\* A111 A960 C710 D013 D019 D021 D029 D120 D199 H4 H401 H481 H5  
 H542 H8 J0 J012 J1 J112 J5 J522 M280 M313 M321 M332 M343 M383  
 M391 M411 M431 M512 M520 M530 M540 M630 M782 Q233 M905 M904  
 DCN: R04193-K R04193-M  
 DCR: 91814-K 91814-M  
 M2 \*31\* D015 D932 H2 H212 J5 J522 L9 L910 M210 M211 M273 M282 M320 M412  
 M431 M511 M520 M530 M540 M782 Q233 M905 M904 M910  
 DCN: R00163-K R00163-M R12974-K R12974-M  
 DCR: 6284-K 6284-M 6284-U

=> d que stat 17  
L5 STR



VAR G1=C/N  
NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE  
L7 21 SEA FILE=REGISTRY SSS FUL L5

100.0% PROCESSED 3813 ITERATIONS  
SEARCH TIME: 00.00.01

21 ANSWERS

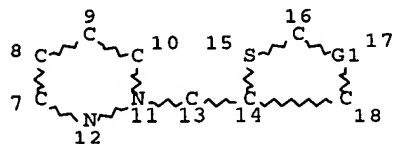
=> d que nos 18  
L5 STR  
L7 21 SEA FILE=REGISTRY SSS FUL L5  
L8 ANALYZE PLU=ON L7 1- LC : 4 TERMS

=> d 18 1-  
L8 ANALYZE L7 1- LC : 4 TERMS

TERM #	# OCC	# DOC	% DOC LC
1	21	21	100.00 CA
2	21	21	100.00 CAPLUS
3	21	21	100.00 TOXCENTER
4	21	21	100.00 USPATFULL

\*\*\*\*\* END OF L8 \*\*\*

=> d que stat 115  
L13 STR



VAR G1=C/N

NODE ATTRIBUTES:

NSPEC IS RC AT 13

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L15 85 SEA FILE=REGISTRY SSS FUL L13

100.0% PROCESSED 661 ITERATIONS

85 ANSWERS

SEARCH TIME: 00.00.01

=> d que nos l16

L13 STR

L15 85 SEA FILE=REGISTRY SSS FUL L13

L16 ANALYZE PLU=ON L15 1- LC : 7 TERMS

=> d l16 1-

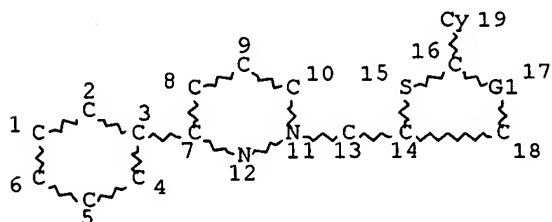
L16 ANALYZE L15 1- LC : 7 TERMS

TERM #	# OCC	# DOC	% DOC	LC
1	85	85	100.00	CA
2	85	85	100.00	CAPLUS
3	65	65	76.47	USPATFULL
4	26	26	30.59	TOXCENTER
5	12	12	14.12	BEILSTEIN
6	7	7	8.24	USPAT2
7	3	3	3.53	CASREACT

\*\*\*\*\* END OF L16\*\*\*

=> d que l35

L5 STR



VAR G1=C/N

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

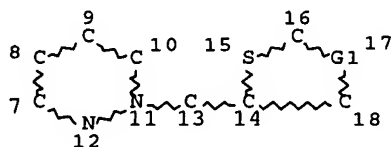
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE

L7 21 SEA FILE=REGISTRY SSS FUL L5

L13 STR



VAR G1=C/N

NODE ATTRIBUTES:

NSPEC IS RC AT 13

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L15 85 SEA FILE=REGISTRY SSS FUL L13

L21 QUE ABB=ON PLU=ON AY<2004 OR PY<2004 OR PRY<2004 OR MY  
<2004 OR REVIEW/DT

L24 QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DI  
ESTERAS?) OR (?PHOSPHODI(W)ESTERAS?)

L27 QUE ABB=ON PLU=ON ?PYRIDAZIN?

L28 QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?

L29 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

L30 32 SEA FILE=HCAPLUS ABB=ON PLU=ON L15

L31 32 SEA FILE=HCAPLUS ABB=ON PLU=ON (L29 OR L30)

L32 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND (L24 OR L27 OR L28)

L33 32 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 OR L32

L34 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND L21

L35 32 SEA FILE=HCAPLUS ABB=ON PLU=ON (L33 OR L34)

=> d his 143

(FILE 'USPATFULL, USPAT2' ENTERED AT 11:51:32 ON 20 DEC 2006)

L43 2 S L37 OR L40 OR L42

=> d que nos 143

L5 STR

L7 21 SEA FILE=REGISTRY SSS FUL L5

L13 STR

L15 85 SEA FILE=REGISTRY SSS FUL L13

L24 QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DI  
ESTERAS?) OR (?PHOSPHODI(W)ESTERAS?)

L37 1 SEA L7

L38 42 SEA L15

L39 42 SEA (L37 OR L38)

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L40 1 SEA L39 AND L24/TI,IT,CC,CT,ST,STP,BI,AB  
L41 36 SEA L39 AND A61P?/IPC  
L42 1 SEA L41 AND A61P?/IPC  
L43 2 SEA L37 OR L40 OR L42

=> d que nos l46

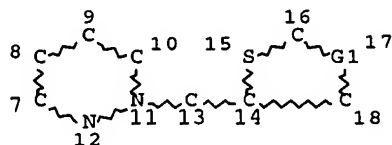
L5 STR  
L7 21 SEA FILE=REGISTRY SSS FUL L5  
L13 STR  
L15 85 SEA FILE=REGISTRY SSS FUL L13  
L44 1 SEA FILE=TOXCENTER ABB=ON PLU=ON L7  
L45 6 SEA FILE=TOXCENTER ABB=ON PLU=ON L15  
L46 6 SEA FILE=TOXCENTER ABB=ON PLU=ON (L44 OR L45)

=> d que nos l48

L13 STR  
L15 85 SEA FILE=REGISTRY SSS FUL L13  
L23 3 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND CASREACT/LC  
L48 3 SEA FILE=CASREACT ABB=ON PLU=ON L23

=> d que stat l49

L13 STR



VAR G1=C/N

NODE ATTRIBUTES:

NSPEC IS RC AT 13  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L49 17 SEA FILE=BEILSTEIN SSS FUL L13

100.0% PROCESSED 31 ITERATIONS  
SEARCH TIME: 00.00.05

17 ANSWERS

=> d his l49-l51

(FILE 'CASREACT' ENTERED AT 11:55:28 ON 20 DEC 2006)  
SAVE TEMP L48 JAI503CRXB/A

FILE 'STNGUIDE' ENTERED AT 11:56:11 ON 20 DEC 2006

FILE 'BEILSTEIN' ENTERED AT 11:56:55 ON 20 DEC 2006

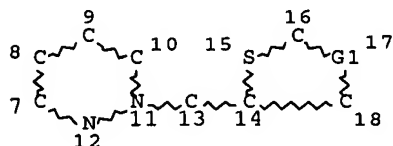
10/518,503

L49 17 S L13 FUL  
SAVE TEMP L49 JAI503BEIP/A  
L50 1 S L49 NOT BABSAN/FA  
SELECT L49 1- BABSAN

FILE 'BABS' ENTERED AT 11:58:18 ON 20 DEC 2006  
L51 6 S E13-E18/AN

=> d que 151  
L51 6 SEA FILE=BABS ABB=ON PLU=ON (5596494/AN OR 6388164/AN OR  
5856247/AN OR 6347066/AN OR 6428743/AN OR 6531693/AN)

=> d que stat 153  
L13 STR



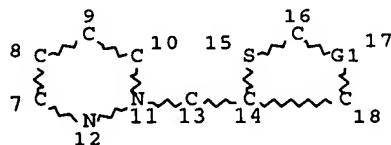
VAR G1=C/N  
NODE ATTRIBUTES:  
NSPEC IS RC AT 13  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE  
L53 2 SEA FILE=CHEMINFORMRX SSS FUL L13 ( 6 REACTIONS)

100.0% DONE 25 VERIFIED 6 HIT RXNS 2 DOCS  
SEARCH TIME: 00.00.04

=> d que stat 155  
L13 STR



VAR G1=C/N  
NODE ATTRIBUTES:  
NSPEC IS RC AT 13  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 12

## STEREO ATTRIBUTES: NONE

L55 35 SEA FILE=WPIX SSS FUL L13

100.0% PROCESSED 40 ITERATIONS  
SEARCH TIME: 00.00.01

35 ANSWERS

=> d his 155-158

(FILE 'WPIX' ENTERED AT 12:00:45 ON 20 DEC 2006)

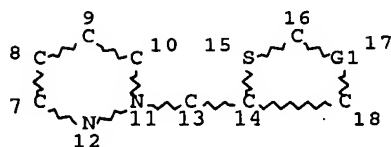
L55 35 S L13 FUL  
SAVE TEMP L55 JAI503WPIS/A  
SELECT L55 1- SDCN  
L56 11 S E19-E53/DCN  
L57 11 S L55/DCR  
L58 11 S L56-L57

=> d que nos 158

L13 STR  
L55 35 SEA FILE=WPIX SSS FUL L13  
L56 11 SEA FILE=WPIX ABB=ON PLU=ON (RACQNP/DCN OR RACVZA/DCN OR  
RACVZB/DCN OR RACVZC/DCN OR RACVZD/DCN OR RACVZE/DCN OR  
RACVZF/DCN OR RACVZG/DCN OR RACVZH/DCN OR RACVZI/DCN OR  
RACVZM/DCN OR RACVZN/DCN OR RACVZO/DCN OR RACVZP/DCN OR  
RACVZ3/DCN OR RACVZ4/DCN OR RACVZ5/DCN OR RACVZ6/DCN OR  
RACVZ7/DCN OR RACVZ8/DCN OR RACVZ9/DCN OR RANV5C/DCN OR  
RANV5G/DCN OR RANV5P/DCN OR RANV5Q/DCN OR RANV6F/DCN OR  
RANV66/DCN OR RA1KDF/DCN OR RA1RZ6/DCN OR RA4W3Q/DCN OR  
RA4XH0/DCN OR RA4X3I/DCN OR RA4X4A/DCN OR RA4X4D/DCN OR  
RA6SZ8/DCN)  
L57 11 SEA FILE=WPIX ABB=ON PLU=ON L55/DCR  
L58 11 SEA FILE=WPIX ABB=ON PLU=ON (L56 OR L57)

=> d que stat 195

L13 STR



VAR G1=C/N

## NODE ATTRIBUTES:

NSPEC IS RC AT 13  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 12

10/518,503

STEREO ATTRIBUTES: NONE

L95 57 SEA FILE=MARPAT SSS FUL L13

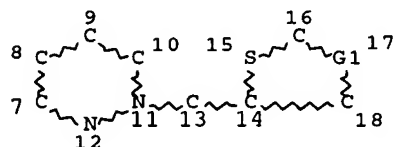
100.0% PROCESSED 6125 ITERATIONS

57 ANSWERS

SEARCH TIME: 00.00.03

=> d que stat l98

L13 STR



VAR G1=C/N

NODE ATTRIBUTES:

NSPEC IS RC AT 13

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

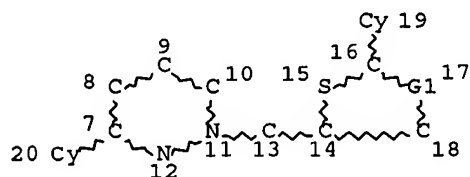
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L95 57 SEA FILE=MARPAT SSS FUL L13

L96 STR



VAR G1=C/N

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

MLEVEL IS ANY AT 19 20

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L98 2 SEA FILE=MARPAT SUB=L95 SSS FUL L96

100.0% PROCESSED 54 ITERATIONS

2 ANSWERS

SEARCH TIME: 00.00.01

=&gt; d que 171

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L24      QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DI
ESTERAS?) OR (?PHOSPHODI(W)ESTERAS?)
L28      QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?
L65      QUE ABB=ON PLU=ON PYRIDAZINES+PFT,OLD,NEW,NT/CT
L66      QUE ABB=ON PLU=ON THIOPHENES+PFT,OLD,NEW,NT/CT
L67      QUE ABB=ON PLU=ON THIAZOLES+PFT,OLD,NEW,NT/CT
L68      257 SEA FILE=MEDLINE ABB=ON PLU=ON L65 AND (L66 OR L67 OR L28)
L69      QUE ABB=ON PLU=ON "PHOSPHODIESTERASE INHIBITORS"+PFT,O
LD,NEW,NT/CT
L70      QUE ABB=ON PLU=ON "PHOSPHODIESTERASES/ANTAGONISTS & IN
HIBITORS"+PFT,OLD,NEW,NT/CT
L71      11 SEA FILE=MEDLINE ABB=ON PLU=ON L68 AND (L24 OR (L69 OR L70))

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=&gt; d que 187

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L24      QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DI
ESTERAS?) OR (?PHOSPHODI(W)ESTERAS?)
L27      QUE ABB=ON PLU=ON ?PYRIDAZIN?
L28      QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?
L73      QUE ABB=ON PLU=ON "PYRIDAZINE DERIVATIVE"+PFT,OLD,NEW,
NT/CT
L74      QUE ABB=ON PLU=ON "PYRIDAZINONE DERIVATIVE"+PFT,OLD,NE
W,NT/CT
L75      QUE ABB=ON PLU=ON "THIAZOLE DERIVATIVE"+PFT,OLD,NEW,NT
/CT
L76      QUE ABB=ON PLU=ON "THIOPHENE DERIVATIVE"+PFT,OLD,NEW,N
T/CT
L77      217 SEA FILE=EMBASE ABB=ON PLU=ON (L73 OR L74) AND ((L75 OR L76)
OR L28)
L78      QUE ABB=ON PLU=ON "PHOSPHODIESTERASE INHIBITOR"+PFT,OL
D,NEW,NT/CT
L83      49 SEA FILE=EMBASE ABB=ON PLU=ON L27(5A)L28
L84      0 SEA FILE=EMBASE ABB=ON PLU=ON L83 AND L78
L85      14 SEA FILE=EMBASE ABB=ON PLU=ON L77 AND L83
L86      0 SEA FILE=EMBASE ABB=ON PLU=ON L83 AND L24
L87      14 SEA FILE=EMBASE ABB=ON PLU=ON (L84 OR L85 OR L86)

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=&gt; d his 192

(FILE 'BIOSIS, PASCAL, JICST-EPLUS, JAPIO, LIFESCI, BIOENG, BIOTECHNO,  
BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED  
AT 12:26:38 ON 20 DEC 2006)

L92 1 S L91 AND L24

=&gt; d que 192

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L24      QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DI
ESTERAS?) OR (?PHOSPHODI(W)ESTERAS?)
L27      QUE ABB=ON PLU=ON ?PYRIDAZIN?
L28      QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?
L91      423 SEA L27(7A) L28
L92      1 SEA L91 AND L24

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=> dup rem 135 143 146 148 151 153 158 198 171 187 192  
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PROCESSING COMPLETED FOR L35  
PROCESSING COMPLETED FOR L43  
PROCESSING COMPLETED FOR L46  
PROCESSING COMPLETED FOR L48  
PROCESSING COMPLETED FOR L51  
PROCESSING COMPLETED FOR L53  
PROCESSING COMPLETED FOR L58  
PROCESSING COMPLETED FOR L98  
PROCESSING COMPLETED FOR L71  
PROCESSING COMPLETED FOR L87  
PROCESSING COMPLETED FOR L92

L99 69 DUP REM L35 L43 L46 L48 L51 L53 L58 L98 L71 L87... (21 DUPLICATES  
REMOVED)

ANSWERS '1-32' FROM FILE HCAPLUS  
ANSWERS '33-34' FROM FILE USPATFULL  
ANSWER '35' FROM FILE TOXCENTER  
ANSWERS '36-37' FROM FILE CHEMINFORMRX  
ANSWERS '38-42' FROM FILE WPIX  
ANSWER '43' FROM FILE MARPAT  
ANSWERS '44-54' FROM FILE MEDLINE  
ANSWERS '55-68' FROM FILE EMBASE  
ANSWER '69' FROM FILE DRUGU

10/518,503

=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE, DRUGU, MARPAT' - CONTINUE? (Y)/N:y

L99 ANSWER 1 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1  
 ACCESSION NUMBER: 2006:886453 HCAPLUS Full-text  
 DOCUMENT NUMBER: 145:292730  
 TITLE: Preparation of Naphthalene derivatives as modulators of the glucocorticoid receptor  
 INVENTOR(S): Rafferty, Stephen William; Turnbull, Philip Stewart; Stewart, Eugene Lee; Caldwell, Richard Dana  
 PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA  
 SOURCE: PCT Int. Appl., 249pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006091592	A1	20060831	WO 2006-US6096	20060221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: US 2005-655603P P 20050223

OTHER SOURCE(S): MARPAT 145:292730

ED Entered STN: 31 Aug 2006

AB Naphthalene derivs. I, wherein n is an integer from 1-4; R1 is cyano or nitro; Y is a carbonyl; Z is an alkylene or an (un)substituted alkylene ether; ; R2 is alkyl, cyano, (un)substituted cycloalkyl, (un)substituted aryl, (un)substituted heteroaryl, etc; m and o are 0 or 1 are prepared for use in treating diseases related to that are modulation of the glucocorticoid receptor. Thus, II was prepared and tested in a variety of biol. studies, including, but not limited to glucocorticoid, androgen and progesterone receptor fluorescence polarization assays; cellular tyrosine aminotransferase assay and an in vivo gluconeogenesis model on mice (no data). Further, I can be used to treat ailments such as type 2 diabetes, type 1 diabetes, hyperglycemia, insulin resistance, metabolic syndrome X, diabetic dyslipidemia, bipolar disorder (manic depression), drug dependency, sleep disorders, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder.

CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 27, 28, 63

IT	908267-47-0P	908267-50-5P	908267-53-8P	908267-56-1P	908267-59-4P
	908267-61-8P	908267-62-9P	908267-64-1P	908267-67-4P	908267-69-6P
	908267-71-0P	908267-73-2P	908267-75-4P	908267-77-6P	908267-79-8P
	908267-81-2P	908267-83-4P	908267-85-6P	908267-87-8P	908267-88-9P

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908268-01-9P	908268-03-1P	908268-05-3P	908268-07-5P	908268-09-7P
908268-11-1P	908268-13-3P	908268-15-5P	908268-18-8P	908268-20-2P
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908272-42-4P	908272-44-6P	908272-45-7P	908272-46-8P	908272-47-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of naphthalene derivs. as modulators of the glucocorticoid  
receptor)

IT	908272-48-0P	908272-49-1P	908272-50-4P	908272-51-5P	908272-52-6P
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	908272-62-8P	908272-63-9P	908272-64-0P	908272-65-1P	908272-66-2P
	908272-67-3P	908272-68-4P	908272-69-5P	908272-70-8P	908272-71-9P
	908272-72-0P	908272-73-1P	908272-74-2P	908272-75-3P	908272-76-4P
	908272-78-6P	908272-79-7P	908272-80-0P	908272-81-1P	908272-82-2P
	908272-83-3P	908272-84-4P	908272-85-5P	908272-86-6P	908272-87-7P
	908272-88-8P	908272-89-9P	908272-90-2P	908272-91-3P	908272-92-4P
	908272-93-5P	908272-94-6P	908272-95-7P	908272-96-8P	908272-97-9P
	908272-98-0P	908272-99-1P	908273-00-7P	908273-01-8P	908273-03-0P

908273-05-2P	908273-07-4P	908273-10-9P	908273-11-0P	908273-12-1P
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908274-15-7P	908274-16-8P	908274-17-9P	908274-18-0P	908274-19-1P
908274-20-4P	908274-21-5P	908274-22-6P	908274-23-7P	

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of naphthalene derivs. as modulators of the glucocorticoid receptor)

IT 60-12-8, 2-(Phenyl)ethanol 66-25-1, Hexanal 66-77-3, 1-Naphthalenecarboxaldehyde 66-99-9, 2-Naphthalenecarboxaldehyde 67-36-7 79-30-1, Isobutyryl chloride 89-75-8, 2,4-Dichlorobenzoyl chloride 89-98-5, 2-Chlorobenzaldehyde 93-25-4 93-40-3 95-48-7, o-Cresol, reactions 98-88-4, Benzoyl chloride 100-07-2 103-80-0, Phenylacetyl chloride 104-53-0, 3-Phenylpropanal 104-87-0, 4-Methylbenzaldehyde 104-88-1, 4-Chlorobenzaldehyde, reactions 104-97-2, Cyclopentanepropanoyl chloride 105-07-7, 4-Cyanobenzaldehyde 106-44-5, p-Cresol, reactions 108-12-3, 3-Methylbutanoyl chloride 108-43-0, 3-Chlorophenol 108-95-2, Phenol, reactions 109-64-8, 1,3-Dibromopropane 110-52-1, 1,4-Dibromobutane 111-24-0, 1,5-Dibromopentane 122-03-2, 4-(1-Methylethyl)benzaldehyde 123-11-5, reactions 135-02-4 141-75-3, Butanoyl chloride 312-94-7, 2-(Trifluoromethyl)benzoyl chloride 329-15-7, 4-(Trifluoromethyl)benzoyl chloride 351-35-9, [3-(Trifluoromethyl)phenyl]acetic acid 393-52-2, 2-Fluorobenzoyl chloride 401-95-6, 3,5-Bis(trifluoromethyl)benzaldehyde 405-50-5, (4-Fluorophenyl)acetic acid 446-52-6, 2-Fluorobenzaldehyde 447-61-0, 2-(Trifluoromethyl)benzaldehyde 451-82-1, (2-Fluorophenyl)acetic acid 454-89-7, 3-(Trifluoromethyl)benzaldehyde 455-01-6, 2-[3-(Trifluoromethyl)phenyl]ethanol 455-19-6, 4-(Trifluoromethyl)benzaldehyde 456-48-4, 3-Fluorobenzaldehyde 458-45-7, 3-(3-Fluorophenyl)propanoic acid 459-31-4, 3-(4-Fluorophenyl)propanoic acid 459-57-4, 4-Fluorobenzaldehyde 498-62-4, 3-Thiophenecarboxaldehyde 500-22-1, 3-Pyridinecarboxaldehyde 527-69-5, 2-Furancarbonyl chloride 529-20-4, 2-Methylbenzaldehyde 581-96-4, (2-Naphthalenyl)acetic acid 585-50-2 586-75-4, 4-Bromobenzoyl chloride 587-04-2, 3-Chlorobenzaldehyde 591-31-1 605-61-8, 1-Chloro-4-nitronaphthalene 606-83-7, 3,3-Diphenylpropanoic acid 613-45-6 620-02-0, 5-Methyl-2-furancarboxaldehyde 620-23-5, 3-Methylbenzaldehyde 621-36-3, (3-Methylphenyl)acetic acid 622-47-9, (4-Methylphenyl)acetic acid 638-29-9, Pentanoyl chloride 644-36-0, (2-Methylphenyl)acetic acid 645-45-4, Benzenepropanoyl chloride 653-21-4, (Pentafluorophenyl)acetic acid 659-28-9 699-02-5, 2-(4-Methylphenyl)ethanol 701-99-5,

(Phenyloxy)acetyl chloride 772-14-5, (3R)-3-Phenylbutanoic acid  
 773-99-9, 2-(1-Naphthalenyl)ethanol 872-85-5, 4-Pyridinecarboxaldehyde  
 874-60-2, 4-Methylbenzoyl chloride 879-18-5, 1-Naphthalenecarbonyl  
 chloride 933-88-0, 2-Methylbenzoyl chloride 935-13-7, 2-Furanpropanoic  
 acid 940-31-8 1074-16-4, 2-(2-Bromophenyl)ethanol 1121-60-4,  
 2-Pyridinecarboxaldehyde 1122-72-1, 6-Methyl-2-pyridinecarboxaldehyde  
 1122-91-4, 4-Bromobenzaldehyde 1122-99-2, Cyclopentylacetyl chloride  
 1200-14-2, 4-Butylbenzaldehyde 1505-50-6, 3-(4-Methylphenyl)propanoic  
 acid 1643-26-1, 3-(2-Fluorophenyl)propanoic acid 1643-28-3,  
 3-(2-Chlorophenyl)propanoic acid 1643-30-7, 3-(4-Bromophenyl)propanoic  
 acid 1710-98-1, 4-(1,1-Dimethylethyl)benzoyl chloride 1711-05-3  
 1711-06-4, 3-Methylbenzoyl chloride 1711-07-5, 3-Fluorobenzoyl chloride  
 1711-09-7, 3-Bromobenzoyl chloride 1711-11-1, 3-Cyanobenzoyl chloride  
 1798-09-0 1871-76-7, Diphenylacetyl chloride 1875-88-3,  
 2-(4-Chlorophenyl)ethanol 1875-89-4, 2-(3-Methylphenyl)ethanol  
 1877-73-2, (3-Nitrophenyl)acetic acid 1878-67-7, (3-Bromophenyl)acetic  
 acid 1878-68-8, (4-Bromophenyl)acetic acid 1899-24-7,  
 5-Bromo-2-furancarboxaldehyde 1912-48-7, (1-Methyl-1H-indol-3-yl)acetic  
 acid 1918-77-0, (2-Thienyl)acetic acid 1929-29-9 2043-61-0,  
 Cyclohexanecarboxaldehyde 2243-83-6, 2-Naphthalenecarbonyl chloride  
 2251-65-2, 3-(Trifluoromethyl)benzoyl chloride 2719-27-9,  
 Cyclohexanecarbonyl chloride 2745-26-8, (2-Furanyl)acetic acid  
 2815-95-4, 1,3-Benzodioxole-5-propanoic acid 2881-63-2 3034-50-2,  
 1H-Imidazole-4-carboxaldehyde 3038-48-0, [2-  
 (Trifluoromethyl)phenyl]acetic acid 3132-99-8, 3-Bromobenzaldehyde  
 3249-68-1, Ethyl 3-oxohexanoate 3446-89-7, 4-(Methylthio)benzaldehyde  
 3457-45-2, 4-Acetylbenzaldehyde 3920-50-1, 1H-Pyrazole-3-carboxaldehyde  
 4023-34-1, Cyclopropanecarbonyl chloride 4315-07-5 4524-93-0,  
 Cyclopentanecarbonyl chloride 4593-90-2, 3-Phenylbutanoic acid  
 4693-91-8 4701-17-1, 5-Bromo-2-thiophenecarboxaldehyde  
 4748-78-1, 4-Ethylbenzaldehyde 4919-33-9 4949-44-4, Ethyl  
 3-oxopentanoate 5006-22-4, Cyclobutanecarbonyl chloride 5020-41-7  
 5238-27-7, 2-Methylpentanoyl chloride 5271-67-0, 2-  
Thiophenecarbonyl chloride 5331-42-0 5398-77-6,  
 4-(Methylsulfonyl)benzaldehyde 5623-81-4, Cyclopentylacetaldehyde  
 5736-88-9 5779-95-3, 3,5-Dimethylbenzaldehyde 5807-30-7,  
 (3,4-Dichlorophenyl)acetic acid 5834-16-2, 3-Methyl-2-  
thiophenecarboxaldehyde 6002-15-9, 1-Phenyl-1H-imidazole-2-  
 carboxaldehyde 6068-72-0, 4-Cyanobenzoyl chloride 6287-38-3,  
 3,4-Dichlorobenzaldehyde 6342-77-4 6469-32-5 6630-33-7,  
 2-Bromobenzaldehyde 6654-36-0, Methyl 6-oxohexanoate 6834-42-0  
 6950-92-1 6964-21-2, (3-Thienyl)acetic acid 7065-46-5 7152-15-0,  
 Ethyl 4-methyl-3-oxopentanoate 7154-66-7, 2-Bromobenzoyl chloride  
 7311-34-4 7468-67-9, 2-Cyanobenzaldehyde 7589-27-7,  
 2-(4-Fluorophenyl)ethanol 10031-82-0 10111-08-7, 1H-Imidazole-2-  
 carboxaldehyde 10203-08-4, 3,5-Dichlorobenzaldehyde 10516-71-9  
 10551-58-3 13679-70-4, 5-Methyl-2-thiophenecarboxaldehyde  
 13750-81-7, 1-Methyl-1H-imidazole-2-carboxaldehyde 13794-14-4  
 13916-99-9, 4-Fluoro-1-naphthalenecarbonitrile 15115-58-9 16251-77-7,  
 3-Phenylbutanal 16340-68-4, 2,2,3,3-Tetramethylcyclopropanecarboxaldeh  
 yde 16681-68-8, 1H-1,2,3-Triazole-4-carboxaldehyde 18698-96-9,  
 (2-Iodophenyl)acetic acid 18698-97-0, (2-Bromophenyl)acetic acid  
 18791-75-8, 4-Bromo-2-thiophenecarboxaldehyde 18791-79-2,  
 5-Bromo-3-thiophenecarboxaldehyde 19819-95-5,  
 2-(2-Chlorophenyl)ethanol 19819-98-8, 2-(2-Methylphenyl)ethanol  
 19955-99-8 21615-34-9 21640-48-2, 3-(3-Chlorophenyl)propanoic acid  
 22047-88-7 22084-89-5, 3-(2-Methylphenyl)propanoic acid 22545-15-9  
 22924-15-8 23074-10-4, 5-Ethyl-2-furancarboxaldehyde 24964-64-5,  
 3-Cyanobenzaldehyde 25016-09-5, 1,3-Dimethyl-1H-pyrazole-5-  
 carboxaldehyde 25026-34-0, 4-(Chlorophenyl)acetyl chloride 25173-68-6,

3-(3,4-Dichlorophenyl)propanoic acid 25563-02-4 26033-20-5  
 26510-52-1, Ethyl 3-oxo-3-(2-pyridinyl)propanoate 27006-76-4,  
 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carboxaldehyde 28229-69-8,  
 2-(3-Bromophenyl)ethanol 28752-82-1 30595-79-0, 2-(2,6-Dichlorophenyl)ethanol 32085-88-4, 3,5-Difluorobenzaldehyde 32852-81-6  
 32857-62-8, [4-(Trifluoromethyl)phenyl]acetic acid 32863-32-4,  
 2,1,3-Benzoxadiazole-4-carboxaldehyde 33166-79-9 33224-99-6  
 33863-86-4 35344-95-7, 1H-Pyrazole-4-carboxaldehyde 35364-79-5,  
 2-(3,4-Dichlorophenyl)ethanol 36823-88-8 36854-57-6, 2-Phenylbutanoyl chloride 36878-91-8 37777-76-7, (2-Chloro-6-fluorophenyl)acetic acid 39515-51-0 42287-90-1, 3-(3-Bromophenyl)propanoic acid 51748-27-7,  
 3-[(Trifluoromethyl)thio]benzaldehyde 52022-77-2, 2-(3-Nitrophenyl)ethanol 52059-53-7, 2-(3-Fluorophenyl)ethanol 52130-30-0,  
 5-[3-(Trifluoromethyl)phenyl]-2-furancarboxaldehyde 52480-43-0,  
 4,5-Dimethyl-2-furancarboxaldehyde 52771-21-8 53473-36-2,  
 3-[4-(Trifluoromethyl)phenyl]propanoic acid 54221-96-4 54605-72-0  
 55116-09-1, 2-(Bromophenyl)acetyl chloride 56990-02-4,  
 3,5-Dibromobenzaldehyde 57204-65-6 57612-86-9, 3-Isoxazoleacetic acid 59664-42-5, 2,4-Bis(trifluoromethyl)benzaldehyde 59756-83-1 63131-29-3  
 65924-65-4, 2-[(1,1-Dimethylethyl)thio]benzaldehyde 68282-47-3,  
 2-Phenyl-1H-imidazole-4-carboxaldehyde 68282-49-5, 2-Butyl-1H-imidazole-4-carboxaldehyde 68282-53-1, 4-Methyl-1H-imidazole-5-carboxaldehyde 69395-13-7, 2-(4-Cyanophenyl)ethanol 70201-43-3, 3-Bromo-4-pyridinecarboxaldehyde 70289-12-2 70416-53-4 72775-83-8 78738-39-3  
 81156-68-5, 2-(2,4-Dichlorophenyl)ethanol 81228-09-3,  
 (2,4-Difluorophenyl)acetic acid 83902-00-5 85068-28-6,  
 (2,6-Difluorophenyl)acetic acid 86270-03-3

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of naphthalene derivs. as modulators of the glucocorticoid receptor)

IT 88634-80-4 89479-66-3, 3-Methyl-5-phenyl-4-isoxazolecarboxaldehyde  
 89990-54-5 90176-80-0, 4-Fluoro-2-(trifluoromethyl)benzaldehyde  
 93618-66-7 94022-96-5 94651-33-9 102191-92-4 112641-20-0,  
 2-Fluoro-3-(trifluoromethyl)benzaldehyde 128455-62-9,  
 5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxaldehyde  
 132274-70-5, 1-Phenyl-1H-pyrazole-5-carboxaldehyde 132706-12-8,  
 5-(2-Pyridinyl)-2-thiophenecarboxaldehyde 145689-41-4,  
 (2,3-Difluorophenyl)acetic acid 146624-87-5 149806-06-4,  
 6-Bromo-3-pyridinecarboxaldehyde 161398-36-3 161712-75-0,  
 3-(3,4-Difluorophenyl)propanoic acid 162046-61-9 175136-79-5  
 177985-32-9, (2-Chloro-4-fluorophenyl)acetic acid 179946-32-8  
 181772-16-7 188815-30-7, 3-Fluoro-5-(trifluoromethyl)benzaldehyde  
 195044-13-4 195447-80-4 203302-97-0 212755-76-5 212755-77-6  
 214262-87-0 220239-67-8 252662-37-6 287917-97-9,  
 4-Bromo-1H-pyrazole-3-carboxaldehyde 350988-62-4 395090-68-3  
 886499-74-7 908268-45-1 908269-54-5

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of naphthalene derivs. as modulators of the glucocorticoid receptor)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Aventis Pharma Sa	2003			FR 2835835 A	HCAPLUS
Cadilla, R	2004			WO 2004110978 A	HCAPLUS
IT	<u>908268-47-3P</u>	<u>908268-57-5P</u>	<u>908268-81-5P</u>		
	<u>908268-83-7P</u>	<u>908269-16-9P</u>	<u>908269-36-3P</u>		
	<u>908272-54-8P</u>				

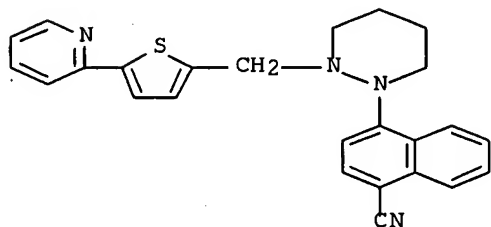
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of naphthalene derivs. as modulators of the glucocorticoid receptor)

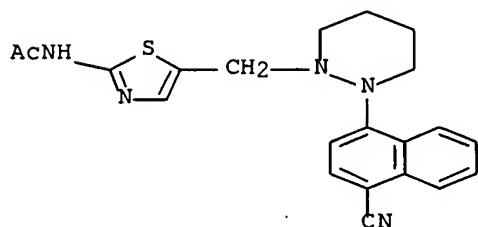
RN 908268-47-3 HCAPLUS

CN 1-Naphthalenecarbonitrile, 4-[tetrahydro-2-[[5-(2-pyridinyl)-2-thienyl]methyl]-1(2H)-pyridazinyl]- (9CI) (CA INDEX NAME)



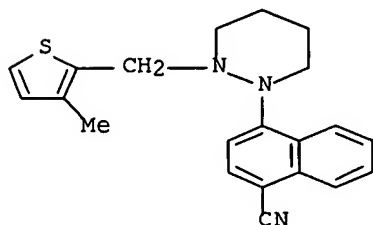
RN 908268-57-5 HCAPLUS

CN Acetamide, N-[5-[[2-(4-cyano-1-naphthalenyl)tetrahydro-1(2H)-pyridazinyl]methyl]-2-thiazolyl]- (9CI) (CA INDEX NAME)



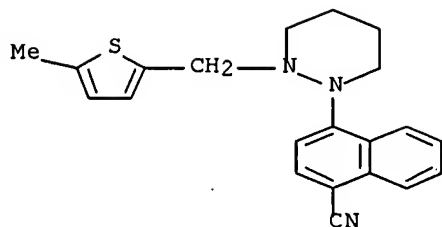
RN 908268-81-5 HCAPLUS

CN 1-Naphthalenecarbonitrile, 4-[tetrahydro-2-[(3-methyl-2-thienyl)methyl]-1(2H)-pyridazinyl]- (9CI) (CA INDEX NAME)



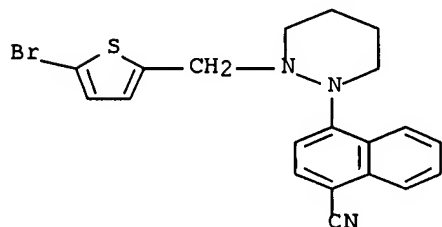
RN 908268-83-7 HCAPLUS

CN 1-Naphthalenecarbonitrile, 4-[tetrahydro-2-[(5-methyl-2-thienyl)methyl]-1(2H)-pyridazinyl]- (9CI) (CA INDEX NAME)



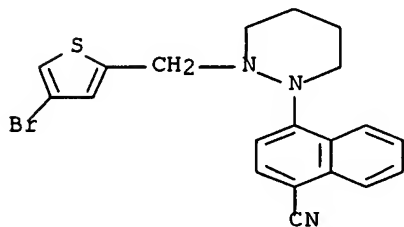
RN 908269-16-9 HCAPLUS

CN 1-Naphthalenecarbonitrile, 4-[2-[(5-bromo-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]- (9CI) (CA INDEX NAME)



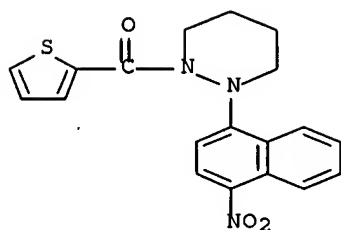
RN 908269-36-3 HCAPLUS

CN 1-Naphthalenecarbonitrile, 4-[2-[(4-bromo-2-thienyl)methyl]tetrahydro-1(2H)-pyridazinyl]- (9CI) (CA INDEX NAME)



RN 908272-54-8 HCAPLUS

CN Pyridazine, hexahydro-1-(4-nitro-1-naphthalenyl)-2-(2-thienylcarbonyl)- (9CI) (CA INDEX NAME)



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L99 ANSWER 2 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:2882 HCAPLUS Full-text

DOCUMENT NUMBER: 140:77154

TITLE: Preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia

INVENTOR(S): Egggenweiler, Hans-Michael; Wolf, Michael

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 125 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000839	A1	20031231	WO 2003-EP4434	20030428 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10227269	A1	20040108	DE 2002-10227269	20020619 <--
CA 2489902	A1	20031231	CA 2003-2489902	20030428 <--
AU 2003232215	A1	20040106	AU 2003-232215	20030428 <--
BR 2003011879	A	20050315	BR 2003-11879	20030428 <--
EP 1513837	A1	20050316	EP 2003-760583	20030428 <--
EP 1513837	B1	20060830		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1662529	A	20050831	CN 2003-814060	20030428 <--
JP 2005530825	T	20051013	JP 2004-514623	20030428 <--
AT 338041	T	20060915	AT 2003-760583	20030428 <--

US 2005222160 A1 20051006 US 2004-518503 20041220 <--  
 PRIORITY APPLN. INFO.: DE 2002-10227269 A 20020619 <--  
 WO 2003-EP4434 W 20030428 <--

OTHER SOURCE(S): MARPAT 140:77154

ED Entered STN: 02 Jan 2004

AB Title compds. I [R1, R2 = H, OH, OR8, etc.; R8 = A, cycloalkyl, alkenyl, etc.; R3 = H, A"R7, COA"R7, etc.; A = alkyl, alkenyl; R7 = H, CO2H, CONH2, etc.; A" = alkylene, alkenylene, cycloalkylene, etc.; V, W = O, OH with the proviso that if V = O, then W = H, H; B = (un)substituted aromatic isocyclic, heterocyclic e.g., pyridyl, pyridyl-N-oxide, thienyl, etc.; X = N, CR3] their pharmaceutically acceptable salts and formulations were prepared For example, coupling of acid chloride II, e.g., prepared from 4-methyl-2-pyridin-2-ylthiazole-5-carboxylic acid Me ester in 3-steps, and 3-(3-cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine afforded claimed thiazole III. Compds. I are claimed useful as phosphodiesterase IV inhibitors (no data provided) for the treatment of osteoporosis, tumors, cachexia, etc.

IC ICM C07D417-14

ICS C07D417-06; A61K031-50; A61P011-06; A61P019-02; A61P019-10; A61P029-00; A61P035-00

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1, 63

ST osteoporosis prepn phosphodiesterase thiazole  
 inhibition; tumor prepn phosphodiesterase thiazole  
 inhibition; cachexia prepn phosphodiesterase thiazole  
 inhibition

IT Inflammation

(Crohn's disease; preparation of thiazoles as  
 phosphodiesterase IV inhibitors for the treatment of  
 osteoporosis, tumors and cachexia)

IT Intestine, disease

(Crohn's; preparation of thiazoles as phosphodiesterase  
 IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT Dermatitis

(atopic; preparation of thiazoles as phosphodiesterase  
 IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT Bronchi, disease

Inflammation

(chronic bronchitis; preparation of thiazoles as  
 phosphodiesterase IV inhibitors for the treatment of  
 osteoporosis, tumors and cachexia)

IT Neoplasm

(metastasis; preparation of thiazoles as phosphodiesterase  
 IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT AIDS (disease)

Allergy

Allergy inhibitors

Anti-AIDS agents

Anti-inflammatory agents

Antiartherosclerotics

Antiasthmatics

Antidiabetic agents

Antirheumatic agents

Antitumor agents

Arteriosclerosis

Asthma

Autoimmune disease

Cachexia

Cardiovascular agents

Diabetes mellitus

Heart, disease

Human  
 Inflammation  
 Multiple sclerosis  
 Neoplasm  
 Osteoporosis  
 Psoriasis  
 Rheumatoid arthritis  
 Sepsis  
 Skin, disease

(preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT Inflammation

Intestine, disease

(ulcerative colitis; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 640743-35-7P 640743-36-8P 640743-37-9P

640743-38-0P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-39-1P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-40-4P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-41-5P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-42-6P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-43-7P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-44-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-45-9P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-46-0P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-47-1P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-48-2P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-49-3P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-50-6P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-phenylthiazol-5-yl)methanone 640743-51-7P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-methoxyphenyl)thiazol-5-yl)methanone 640743-52-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-aminophenyl)thiazol-5-yl)methanone 640743-53-9P 640743-54-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 640743-56-2P 640743-57-3P 640743-58-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 9036-21-9, Phosphodiesterase IV

RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

IT 109-77-3, Propanedinitrile 937-14-4 257876-11-2 438627-45-3, 3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-55-1, 4-Methyl-2-pyridin-2-ylthiazole-5-carboxylic acid methyl ester 640743-59-5, 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-60-8, 3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine 640743-61-9 640743-62-0 640743-63-1 640743-64-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Merck Patent GmbH	1997			EP 0763534 A	HCAPLUS
Werner, K	1998			WO 9806704 A	HCAPLUS

IT 640743-35-7P 640743-36-8P 640743-37-9P

640743-38-0P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol

-5-yl)methanone 640743-39-1P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone 640743-40-4P,

1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone

640743-41-5P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol

-5-yl)methanone 640743-42-6P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-

pyridin-2-ylthiazol-5-yl)methanone 640743-43-7P, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin

-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone 640743-44-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-

pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-45-9P, 1-[3-(3-Isopropoxy-4-

methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone 640743-46-0P,

1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone

640743-47-1P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-

ylthiazol-5-yl)methanone 640743-48-2P, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin

-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-49-3P, 1-[3-(3-Cyclopentyloxy-4-

methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone 640743-50-6P

, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-phenylthiazol-5-yl)methanone

640743-51-7P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-methoxyphenyl)thiazol

-5-yl)methanone 640743-52-8P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-

10/518,503

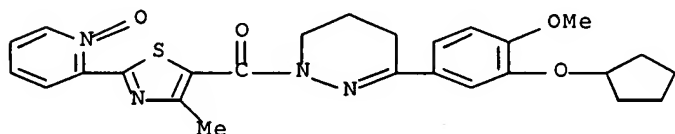
5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-aminophenyl)  
thiazol-5-yl]methanone **640743-53-9P** **640743-54-0P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(drug candidate; preparation of **thiazoles** as  
**phosphodiesterase** IV inhibitors for the treatment of  
osteoporosis, tumors and cachexia)

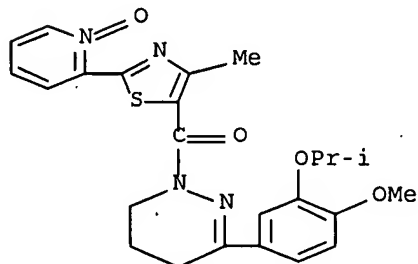
RN 640743-35-7 HCAPLUS

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-  
[[4-methyl-2-(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX  
NAME)



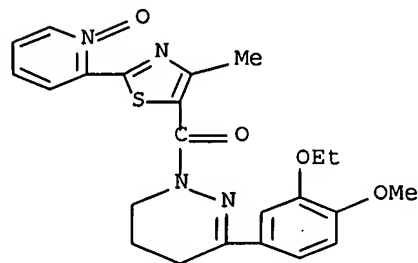
RN 640743-36-8 HCAPLUS

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-  
[[4-methyl-2-(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX  
NAME)



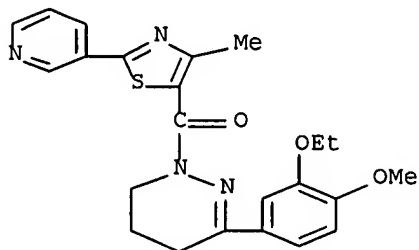
RN 640743-37-9 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-  
(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



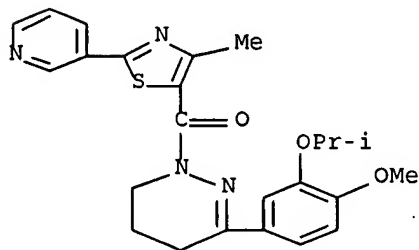
RN 640743-38-0 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



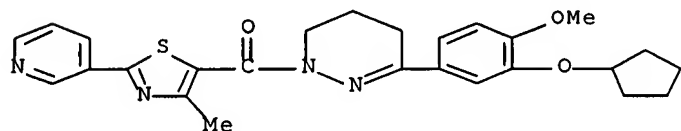
RN 640743-39-1 HCAPLUS

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



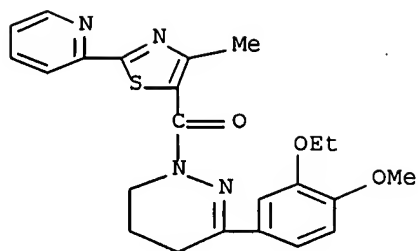
RN 640743-40-4 HCAPLUS

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



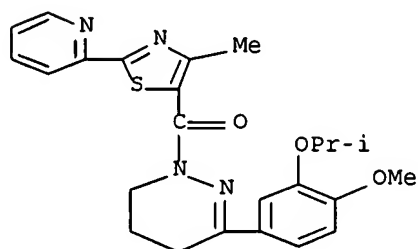
RN 640743-41-5 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



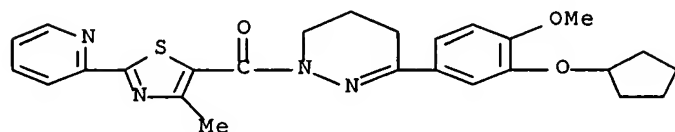
RN 640743-42-6 HCAPLUS

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



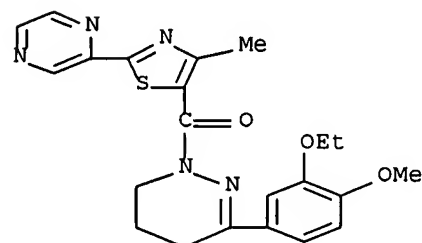
RN 640743-43-7 HCAPLUS

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

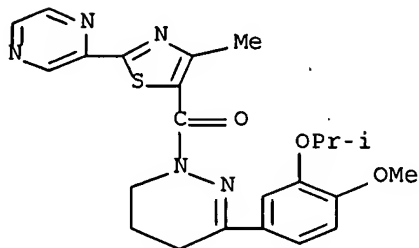


RN 640743-44-8 HCAPLUS

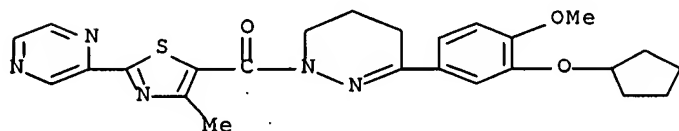
CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[(4-methyl-2-pyrazinyl-5-thiazolyl)carbonyl]- (9CI) (CA INDEX NAME)



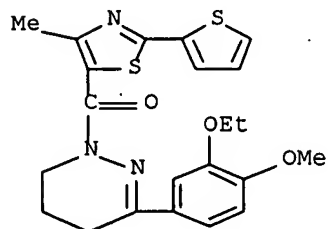
RN 640743-45-9 HCAPLUS

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-  
[[4-methyl-2-pyrazinyl-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

RN 640743-46-0 HCAPLUS

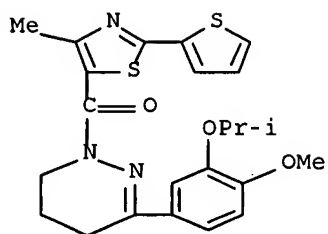
CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-  
[[4-methyl-2-pyrazinyl-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

RN 640743-47-1 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-  
(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

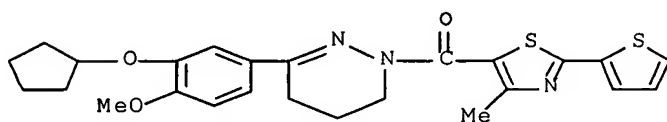
RN 640743-48-2 HCAPLUS

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-  
[[4-methyl-2-(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



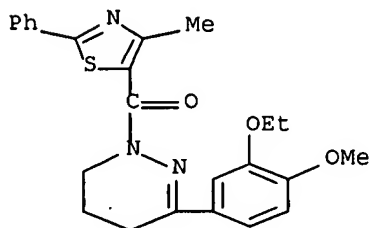
RN 640743-49-3 HCAPLUS

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



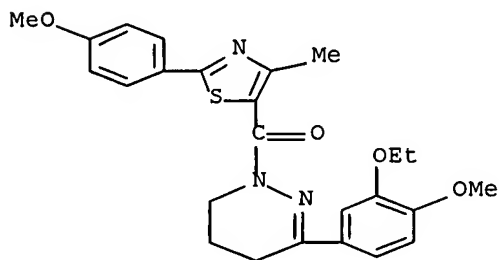
RN 640743-50-6 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[(4-methyl-2-phenyl-5-thiazolyl)carbonyl]- (9CI) (CA INDEX NAME)



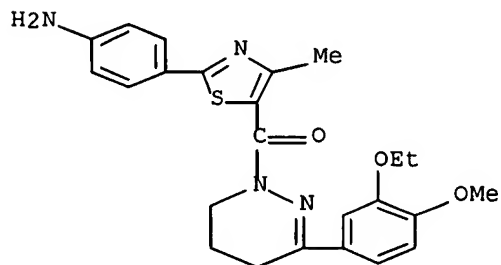
RN 640743-51-7 HCAPLUS

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[2-(4-methoxyphenyl)-4-methyl-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



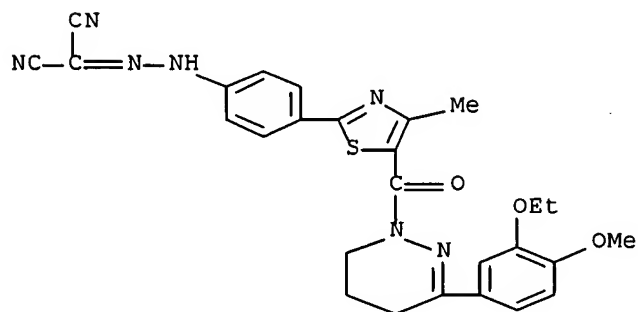
RN 640743-52-8 HCAPLUS

CN Pyridazine, 1-[[2-(4-aminophenyl)-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



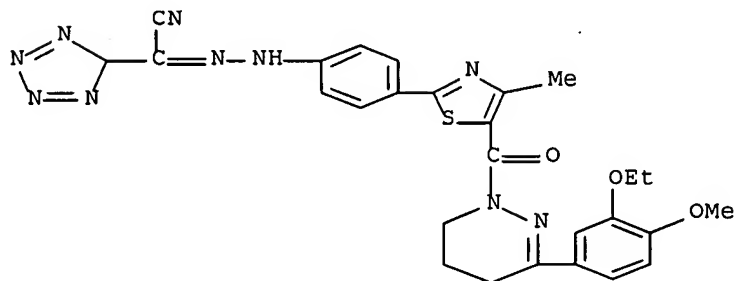
RN 640743-53-9 HCAPLUS

CN Pyridazine, 1-[[2-[4-[(dicyanomethylene)hydrazino]phenyl]-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



RN 640743-54-0 HCAPLUS

CN Pyridazine, 1-[[2-[4-[(cyano-5H-tetrazol-5-ylmethylene)hydrazino]phenyl]-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)

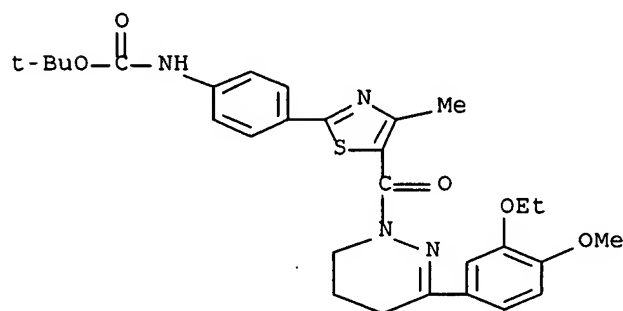


IT 640743-64-2

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of thiazoles as phosphodiesterase IV  
 inhibitors for the treatment of osteoporosis, tumors and cachexia)

RN 640743-64-2 HCAPLUS

CN Carbamic acid, [4-[5-[[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-1(4H)-  
 pyridazinyl]carbonyl]-4-methyl-2-thiazolyl]phenyl]-, 1,1-dimethylethyl  
 ester (9CI) (CA INDEX NAME)



L99 ANSWER 3 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2003:908829 HCAPLUS Full-text

DOCUMENT NUMBER: 140:94001

TITLE: Regioselective reduction of 2-  
 (arylideneamino)isoindole-1,3-diones - synthesis of  
 alkaloid analogues by N-acylhydrazone ion aromatic  
 $\pi$ -cyclization

AUTHOR(S): Fogain-ninkam, Alain; Daich, Adam; Decroix, Bernard;  
 Netchitailo, Pierre

CORPORATE SOURCE: URCOM, EA 3221, UFR des Sciences et Techniques,  
 Universite du Havre, URCOM, EA 3221, UFR des Sciences  
 et Techniques, Le Havre, 76058, Fr.

SOURCE: European Journal of Organic Chemistry (2003  
 ), (21), 4273-4278

CODEN: EJOCFK; ISSN: 1434-193X

PUBLISHER: Wiley-VCH Verlag GmbH &amp; Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 140:94001

ED Entered STN: 20 Nov 2003

AB Hydroxylactams were synthesized by successive regioselective redns. of  
 [(arylmethylene)amino]phthalimides, which were easily available from  
 aminophthalimide and benzaldehyde of thiophenecarboxaldehydes. N-  
 Acylhydrazone ions, generated in the presence of Lewis acid from acetoxy  
 derivs. of hydroxylactams, or in organic acid medium directly from  
 hydroxylactams, induced the expected isoindolophthalazines and  
thienopyridazinoisoindolones. On the other hand, hydroxylactams under acidic  
 conditions gave unexpected N-thienylmethyl-substituted  
thienopyridazinoisoindolones.

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 27, 31

ST isoindolophthalazinone prepn; thienopyridazinoisoindolone prepn;  
 regioselective redn arylimino phthalimide; cyclization regioselective redn

arylimino phthalimide; alkaloid analog prepn cyclization regioselective  
redn arylimino phthalimide

IT 98-03-3, 2-Thiophenecarboxaldehyde 100-52-7, Benzaldehyde,  
reactions 498-62-4, 3-Thiophenecarboxaldehyde 1875-48-5,  
2-Amino-1H-isoindole-1,3(2H)-dione

RL: RCT (Reactant); RACT (Reactant or reagent)

(regioselective reduction of (arylideneamino)isoindolediones and  
preparation of

alkaloid analogs by N-acylhydrazonium ion aromatic  $\pi$ -cyclization)

IT 643752-20-9P 643752-22-1P 643752-24-3P 643752-26-5P  
643752-27-6P 643752-29-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(regioselective reduction of (arylideneamino)isoindolediones and  
preparation of

alkaloid analogs by N-acylhydrazonium ion aromatic  $\pi$ -cyclization)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
=====					
Bartovic, A	2000	37	827	J Heterocyclic Chem	HCAPLUS
Bartovic, A	2000	37	827	J Heterocyclic Chem	HCAPLUS
Borch, R	1971	93	2897	J Am Chem Soc	HCAPLUS
Denmark, S	1988	53	1251	J Org Chem	HCAPLUS
Dhimane, H	1998		1955	Eur J Org Chem	HCAPLUS
Dudley, T	1999	64	1247	J Org Chem	HCAPLUS
Hiemstra, H	1991	2	1047	Comprehensive Organi	
Korenova, A	1998	35	9	J Heterocyclic Chem	HCAPLUS
Metals, E	1997	62	9210	J Org Chem	HCAPLUS
Nelsen, S	1973	14	2321	Tetrahedron Lett	
Othman, M	2000	52	273	Heterocycles	HCAPLUS
Pestellini, V	1978	13	296	Eur J Med Chem	HCAPLUS
Pigeon, P	1998	54	1497	Tetrahedron	HCAPLUS
Pigeon, P	1997	38	1041	Tetrahedron Lett	HCAPLUS
Rutjes, F	1993	49	10027	Tetrahedron	HCAPLUS
Rutjes, F	1993	49	8605	Tetrahedron	HCAPLUS
Rutjes, F	1988	29	6975	Tetrahedron Lett	HCAPLUS
Speckamp, W	2000	56	3817	Tetrahedron	HCAPLUS
Suzuki, H	1995	60	6114	J Org Chem	HCAPLUS
Teerhuis, N	1997	38	155	Tetrahedron Lett	HCAPLUS
Teerhuis, N	1997	38	159	Tetrahedron Lett	HCAPLUS

IT 643752-27-6P

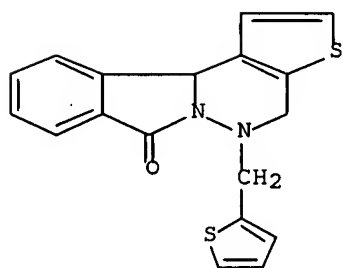
RL: SPN (Synthetic preparation); PREP (Preparation)

(regioselective reduction of (arylideneamino)isoindolediones and  
preparation of

alkaloid analogs by N-acylhydrazonium ion aromatic  $\pi$ -cyclization)

RN 643752-27-6 HCAPLUS

CN Thieno[2',3':4,5]pyridazino[6,1-a]isoindol-7(5H)-one, 4,11b-dihydro-5-(2-  
thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 4 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2003:189365 HCAPLUS Full-text

DOCUMENT NUMBER: 139:78424

TITLE: Pyridazinones as selective cyclooxygenase-2 inhibitors

AUTHOR(S): Li, Chun Sing; Brideau, Christine; Chan, Chi Chung; Savoie, Chantal; Claveau, David; Charleson, Stella; Gordon, Robert; Greig, Gillian; Gauthier, Jacques Yves; Lau, Cheuk K.; Riendeau, Denis; Therien, Michel; Wong, Elizabeth; Prasit, Petpiboon

CORPORATE SOURCE: Merck Frosst Centre for Therapeutic Research, Pointe-Claire-Dorval, QC, 1005, Can.

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(4), 597-600

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:78424

ED Entered STN: 11 Mar 2003

AB Pyridazinone was found to be an excellent core template for selective COX-2 inhibitors. Two potent, selective and orally active COX-2 inhibitors (I and II), which were highly efficacious in rat paw edema and rat pyresis models, have been obtained.

CC 1-3 (Pharmacology)

Section cross-reference(s): 28

ST pyridazinone analog prepn cyclooxygenase 2 inhibitor antiinflammatory

IT Structure-activity relationship

(enzyme-inhibiting; preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

IT Anti-inflammatory agents

(preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

IT 329900-75-6, Cyclooxygenase-2

RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

IT	213763-79-2P	213763-80-5P	213763-81-6P	213763-82-7P	213763-83-8P
	213763-92-9P	213763-96-3P	213763-99-6P	213764-00-2P	213764-01-3P
	<u>213764-05-7P</u>	213764-08-0P	213764-13-7P	213764-14-8P	
	213764-15-9P	221025-57-6P	552865-16-4P	552865-17-5P	552865-18-6P
	552865-19-7P	552865-20-0P	552865-21-1P	552865-22-2P	552865-23-3P
	552865-24-4P	552865-25-5P	552865-26-6P	552865-27-7P	552865-28-8P
	552865-29-9P				

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

IT 67-63-0, 2-Propanol, reactions 74-83-9, Methane, bromo-, reactions 100-39-0, Benzene, (bromomethyl)- 108-86-1, Benzene, bromo-, reactions 108-98-5, Thiophenol, reactions 371-41-5, Phenol, 4-fluoro- 507-19-7, Propane, 2-bromo-2-methyl- 870-63-3, 2-Butene, 1-bromo-3-methyl- 2516-33-8, Cyclopropanemethanol 2550-36-9, Cyclohexane, (bromomethyl)- 4214-79-3 4333-56-6, Cyclopropane, bromo- 5042-30-8, Hydrazine, (2,2,2-trifluoroethyl)- 5720-05-8, Boronic acid, (4-methylphenyl)- 7051-34-5, Cyclopropane, (bromomethyl)- 36982-56-6, Cyclopropane, (2-bromoethyl)- 42082-19-9, Cyclopropane, 1-(bromomethyl)-1-methyl- 45438-73-1, Thiophene, 2-(bromomethyl)- 51598-33-5 51598-64-2 56634-50-5 69966-55-8, Pyridine, 3-(bromomethyl)- 80204-20-2 98546-51-1, Boronic acid, (4-methylthiophenyl)- 131654-56-3, Thiazole, 2-(bromomethyl)- 157672-00-9 162011-90-7 210117-20-7, Cyclopropane, 2-(bromomethyl)-1,1-dimethyl- 313272-18-3 659742-17-3 659742-21-9  
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

IT 162012-28-4P 185147-17-5P 213764-20-6P 213764-23-9P 552865-13-1P 552865-14-2P 552865-15-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

# RETABLE

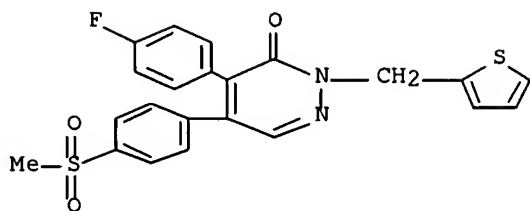
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bombardier, C	2002	89	3-D	Am J Cardiol	
Brideau, C	1996	45	68	Inflamm Res	HCAPLUS
Chan, C	1995	274	1531	J Pharmacol Exp Ther	HCAPLUS
Charette, A	1995	60	1081	J Org Chem	HCAPLUS
Dannhardt, G	2001	36	109	Eur J Med Chem	HCAPLUS
Friesen, R	1998	8	2777	Bioorg Med Chem Lett	HCAPLUS
Jas, G	1991	11	965	Synthesis	
Kargman, S	1996	52	1113	Biochem Pharmacol	HCAPLUS
Li, J	1996	39	1846	J Med Chem	HCAPLUS
Penning, T	1997	40	1347	J Med Chem	HCAPLUS
Pinto, D	1999	9	919	Bioorg Med Chem Lett	HCAPLUS
Prasit, P	1999	9	1773	Bioorg Med Chem Lett	HCAPLUS
Riendeau, D	1997	75	1088	Can J Phys Pharmacol	HCAPLUS
Talley, J	2000	43	775	J Med Chem	HCAPLUS

IT 213764-05-7P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of pyridazinones as selective cyclooxygenase-2 inhibitors)

RN 213764-05-7 HCAPLUS

CN 3(2H)-Pyridazinone, 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 5 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5  
 ACCESSION NUMBER: 2002:106302 HCAPLUS Full-text  
 DOCUMENT NUMBER: 136:294791  
 TITLE: Reaction of 1,4-Phthalazinedione with Furfural:  
 Formation of the [5,6]Benza-3a,7a-diazaindane System  
 via an Unusual Skeletal Rearrangement  
 AUTHOR(S): Amarasekara, Ananda S.; Chandrasekara, Susantha  
 CORPORATE SOURCE: Department of Chemistry, University of Colombo,  
 Colombo, Sri Lanka  
 SOURCE: Organic Letters (2002), 4(5), 773-775  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 136:294791  
 ED Entered STN: 10 Feb 2002  
 AB Oxidation of phthalhydrazide with lead tetraacetate in the presence of  
 furfural or 5-methylfurfural in CH<sub>3</sub>Cl<sub>3</sub> gave the carboxydiazabenzindenediones I  
 (R = H, Me) in 64% and 46% yields, resp. Similar reaction of phthalhydrazide  
 with 2-thiophenecarboxaldehyde gave the (thienylcarbonyl)phthalhydrazide II.  
 CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 ST rearrangement oxidn cyclocondensation phthalhydrazide furfural;  
 thienylcarbonylphthalhydrazide prepn; thiophenecarboxaldehyde  
 oxidn cyclocondensation phthalhydrazide; benzdiazaindanedione carboxy  
 prepn; phthalhydrazide lead tetraacetate oxidn cyclocondensation furfural  
 IT 98-03-3, 2-Thiophenecarboxaldehyde  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of (thienylcarbonyl)phthalhydrazide by oxidation/condensation  
 of thiophenecarboxaldehyde with phthalhydrazide)  
 IT 408535-41-1P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of (thienylcarbonyl)phthalhydrazide by oxidation/condensation  
 of thiophenecarboxaldehyde with phthalhydrazide)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Agmon, I	1986	108	4477	J Am Chem Soc	HCAPLUS
Alder, K	1954	81	585	Ann	
Amarasekara, A	2000	73	267	Bull Chem Soc Jpn	
Baldwin, J	1976		734	J Chem Soc, Chem Com	HCAPLUS
Baldwin, J	1976		736	J Chem Soc, Chem Com	HCAPLUS
Clement, R	1960	27	1115	J Org Chem	
Clement, R	1960	25	1724	J Org Chem	HCAPLUS
Cocharan, J	1996	37	2903	Tetrahedron Lett	

Cookson, R	1962		615	Tetrahedron Lett	HCAPLUS
Cramer, R	1960	79	6215	J Am Chem Soc	
Criegee, R	1965		311	Oxidation in Organic	
Dean, F	1982	31	237	Adv Heterocycl Chem	HCAPLUS
Filer, C	1979	44	285	J Org Chem	HCAPLUS
Friedrich, E	1975	40	720	J Org Chem	HCAPLUS
Johnson, C	1993	26	476	Acc Chem Res	HCAPLUS
Junculev, J	1961	33	59	Croat Chem Acta	
Kealy, T	1962	84	966	J Am Chem Soc	HCAPLUS
Lambert, J	1980	102	3588	J Am Chem Soc	HCAPLUS
Mavoungou-Gomes, L	1967		1764	Bull Soc Chim Fr	HCAPLUS
McClelland, R	1981	46	4345	J Am Chem Soc	HCAPLUS
Sternhell, S	1969	23	236	Q Rev	HCAPLUS
Wong, H	1983	20	1815	Heterocycles	HCAPLUS
Wong, H	1984	22	875	Heterocycles	HCAPLUS
Zaballos-Garcia, E	1997	53	9313	Tetrahedron	HCAPLUS

IT **408535-41-1P**

RL: SPN (Synthetic preparation); PREP (Preparation)

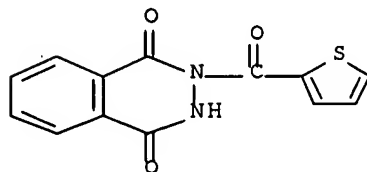
(preparation of (thienylcarbonyl)phthalhydrazide by oxidation/condensation

of

thiophenecarboxaldehyde with phthalhydrazide)

RN 408535-41-1 HCAPLUS

CN 1,4-Phthalazinedione, 2,3-dihydro-2-(2-thienylcarbonyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 6 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2001:489398 HCAPLUS Full-text

DOCUMENT NUMBER: 135:92643

TITLE: Preparation of 1,2,5,10-tetrahydropyridazino  
[4,5-b]quinoline-1,10-diones for the treatment of painINVENTOR(S): Murphy, Megan; Urbanek, Rebecca Ann; Xiao, Wenhua;  
Steelman, Gary Banks; Brown, Dean Gordon; Bare, Thomas  
Michael

PATENT ASSIGNEE(S): Astrazeneca Ab, Swed.

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047925	A1	20010705	WO 2000-SE2609	20001219 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,				
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001025662 A5 20010709 AU 2001-25662 20001219 <--  
EP 1244664 A1 20021002 EP 2000-989117 20001219 <--  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
JP 2003519147 T 20030617 JP 2001-549395 20001219 <--  
EP 1577311 A1 20050921 EP 2005-5708 20001219 <--  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
ZA 2002004779 A 20030915 ZA 2002-4779 20020613 <--  
ZA 2002004781 A 20030915 ZA 2002-4781 20020613 <--  
US 2003153572 A1 20030814 US 2003-168762 20030212 <--  
US 6730675 B2 20040504

PRIORITY APPLN. INFO.:

US 1999-171906P P 19991223 <--  
US 2000-236786P P 20000929 <--  
US 2000-236783P P 20000929 <--  
EP 2000-987935 A3 20001219 <--  
WO 2000-SE2609 W 20001219 <--

OTHER SOURCE(S): MARPAT 135:92643

ED Entered STN: 06 Jul 2001

AB The title compds. [I; R1 = halo; A = (CH<sub>2</sub>)<sub>n</sub> (n = 1-4); D = (un)substituted 5-membered heteroaryl or its benz- derivative], useful for treating pain, were prepared E.g., a multi-step synthesis of I [R1 = 7-Cl; A = CH<sub>2</sub>; D = 2,5-dimethylfuran-3-yl] which showed K<sub>i</sub> of 24.8 nM in test for binding to NMDA receptor glycine site, was given.

IC ICM C07D471-04

ICS A61K031-5025

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST pyridazinoquinolinedione prepn analgesic NMDA receptor glycine site

IT Glutamate receptors

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(NMDA-binding, glycine site; preparation of 1,2,5,10-

tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT Analgesics

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 348088-73-3P 348088-74-4P 348088-75-5P 348088-76-6P  
348088-77-7P 348088-78-8P 348088-79-9P 348088-80-2P  
348088-81-3P 348088-82-4P 348088-83-5P  
348088-84-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 123-75-1, Pyrrolidine, reactions 620-02-0, 5-Methylfurfural 762-42-5, Dimethyl acetylenedicarboxylate 870-46-2, tert-Butylcarbazate 5834-16-2, 3-Methylthiophene-2-carboxaldehyde 5900-58-3, Methyl 2-amino-4-chlorobenzoate 5904-71-2, Methyl 5-formylfuran-2-carboxylate 6141-58-8, Methyl 2-methyl-3-furoate 6148-34-1 13679-70-4, 5-Methylthiophene-2-carboxaldehyde 19788-37-5,

4-(Chloromethyl)-3,5-dimethylisoxazole 22053-74-3, 3-  
**Methylbenzothiophene**-2-carboxaldehyde 24006-09-5 30153-47-0  
 34035-04-6 52480-43-0 348088-91-5

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 1,2,5,10-**tetrahydropyridazino**[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 1003-96-9P 113874-61-6P 147494-01-7P 170143-35-8P 179543-91-0P  
 179543-97-6P 348088-85-7P 348088-86-8P 348088-87-9P 348088-88-0P  
 348088-89-1P 348088-90-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 1,2,5,10-**tetrahydropyridazino**[4,5-b]quinoline-1,10-diones for the treatment of pain)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Zeneca Limited	1995			WO 9511244 A1	HCAPLUS
Zeneca Limited	1996			EP 0736531 A1	HCAPLUS

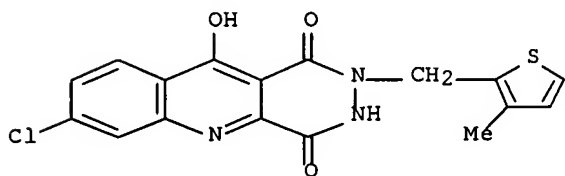
IT **348088-74-4P** **348088-81-3P** **348088-82-4P**  
**348088-83-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-**tetrahydropyridazino**[4,5-b]quinoline-1,10-diones for the treatment of pain)

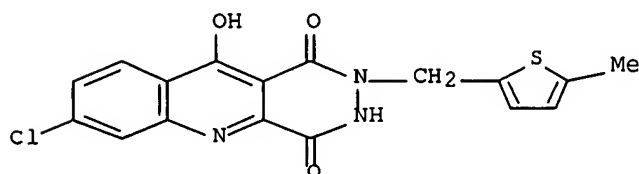
RN 348088-74-4 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4-dione, 7-chloro-2,3-dihydro-10-hydroxy-2-[(3-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



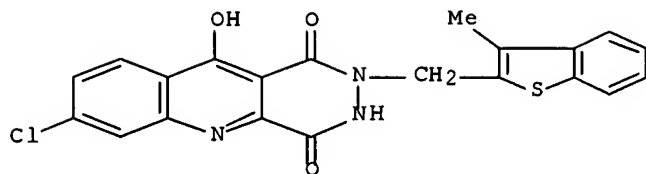
RN 348088-81-3 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4-dione, 7-chloro-2,3-dihydro-10-hydroxy-2-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)

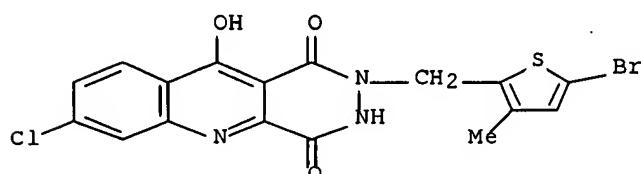


RN 348088-82-4 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4-dione, 7-chloro-2,3-dihydro-10-hydroxy-2-[(3-methylbenzo[b]thien-2-yl)methyl]- (9CI) (CA INDEX NAME)



RN 348088-83-5 HCAPLUS  
 CN Pyridazino[4,5-b]quinoline-1,4-dione, 2-[(5-bromo-3-methyl-2-thienyl)methyl]-7-chloro-2,3-dihydro-10-hydroxy- (9CI) (CA INDEX NAME)



L99 ANSWER 7 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7  
 ACCESSION NUMBER: 2001:489232 HCAPLUS Full-text  
 DOCUMENT NUMBER: 135:92648  
 TITLE: Preparation of 1,2,5,10-tetrahydropyridazino  
 [4,5-b]quinoline-1,10-diones for the treatment of pain  
 INVENTOR(S): Alford, Vernon; Bare, Thomas Michael; Brown, Dean  
 Gordon; McLaren, Frances Marie; Murphy, Megan;  
 Urbanek, Rebecca Ann; Xiao, Wenhua  
 PATENT ASSIGNEE(S): Astrazeneca AB, Swed.  
 SOURCE: PCT Int. Appl., 40 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 7  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047523	A1	20010705	WO 2000-SE2605	20001219 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2394561	A1	20010705	CA 2000-2394561	20001219 <--
AU 2001025660	A5	20010709	AU 2001-25660	20001219 <--
AU 783499	B2	20051103		

BR 2000016646	A	20021008	BR 2000-16646	20001219 <--
EP 1248621	A1	20021016	EP 2000-989115	20001219 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 200300043	A2	20030528	HU 2003-43	20001219 <--
JP 2003518499	T	20030610	JP 2001-548117	20001219 <--
EE 200200348	A	20030815	EE 2002-348	20001219 <--
NZ 519389	A	20040528	NZ 2000-519389	20001219 <--
RU 2238094	C2	20041020	RU 2002-115273	20001219 <--
EP 1577311	A1	20050921	EP 2005-5708	20001219 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CZ 296493	B6	20060315	CZ 2002-2176	20001219 <--
ZA 2002004779	A	20030915	ZA 2002-4779	20020613 <--
ZA 2002004781	A	20030915	ZA 2002-4781	20020613 <--
BG 106832	A	20030331	BG 2002-106832	20020618 <--
NO 2002002990	A	20020820	NO 2002-2990	20020620 <--
US 2003162783	A1	20030828	US 2003-168745	20030128 <--
PRIORITY APPLN. INFO.:				
			US 1999-171906P	P 19991223 <--
			US 2000-236835P	P 20000929 <--
			US 2000-236783P	P 20000929 <--
			EP 2000-987935	A3 20001219 <--
			WO 2000-SE2605	W 20001219 <--

OTHER SOURCE(S): MARPAT 135:92648

ED Entered STN: 06 Jul 2001

AB The title compds. [I; A = (CH<sub>2</sub>)<sub>n</sub> (wherein n = 0-4); D = 5-6 membered heteroaryl or its benz- derivative having 1-3 ring atoms selected from O, N or S; R<sub>1</sub> = halo], useful for the treatment of pain, were prepared E.g., a multi-step synthesis of I.MeSO<sub>3</sub>H [A = CH<sub>2</sub>; n = 1; D = 4-pyridyl; R<sub>1</sub> = 7-Cl] which showed a K<sub>i</sub> of 79 nM in a test for binding to the NMDA receptor glycine site, was given.

IC ICM A61K031-5025

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST pyridazinoquinolinedione prepn analgesic NMDA receptor glycine site

IT Glutamate receptors

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(NMDA-binding, glycine site; preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT Analgesics

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 170142-52-6P 170143-15-4P 170143-16-5P 170143-17-6P  
 348627-82-7P 348627-83-8P 348627-84-9P 348627-85-0P 348627-87-2P  
 348627-88-3P 348627-90-7P 348627-91-8P 348627-93-0P 348627-95-2P  
 348627-96-3P 348627-98-5P 348627-99-6P 348628-04-6P  
 348628-05-7P 348628-06-8P 348628-07-9P 348628-08-0P 348628-09-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 95-15-8, Benzothiophene 98-01-1, 2-Furaldehyde, reactions  
 98-03-3, Thiophene-2-carboxaldehyde 109-08-0, 2-Methylpyrazine  
 123-75-1, Pyrrolidine, reactions 498-60-2, 3-Furaldehyde 498-62-4,  
Thiophene-3-carboxaldehyde 762-42-5, Dimethyl  
 acetylenedicarboxylate 870-46-2, tert-Butyl carbazate 1822-51-1,

4-Picolyl chloride hydrochloride 4265-16-1, Benzofuran-2-carboxaldehyde 4363-93-3, Quinoline-4-carboxaldehyde 5900-58-3, Methyl 2-amino-4-chlorobenzoate 6959-47-3, 2-Picolyl chloride hydrochloride 6959-48-4, 3-Picolyl chloride hydrochloride 10111-08-7, 2-Imidazolecarboxaldehyde 10200-59-6, 2-Thiazolecarboxaldehyde 54198-81-1, 4-Chloromethylpyrimidine 69735-35-9, 5-Bromomethylisoxazole  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 3541-37-5P, Benzo[b]thiophene-2-carboxaldehyde 39204-47-2P,  
 2-Chloromethylpyrazine 113906-60-8P 147494-01-7P 150767-01-4P  
 150767-03-6P 150767-04-7P 162739-66-4P 162739-74-4P 162739-88-0P  
 170143-35-8P 182887-52-1P 182887-56-5P 348628-12-6P 348628-13-7P  
 348628-14-8P 348628-15-9P 348628-16-0P 348628-17-1P 348628-18-2P  
 348628-19-3P 348628-20-6P 348628-21-7P 348628-22-8P 348628-23-9P  
 348628-24-0P 348628-25-1P 348628-26-2P 348628-27-3P 348628-28-4P  
 348628-29-5P 348628-30-8P 348628-31-9P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Zeneca Limited	1995			WO 9511244 A1	HCAPLUS

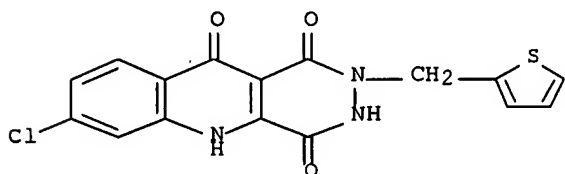
IT 170142-52-6P 348628-04-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

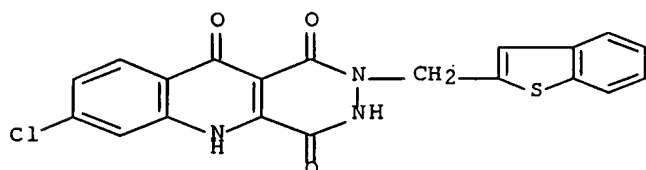
RN 170142-52-6 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 7-chloro-2,3-dihydro-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



RN 348628-04-6 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 2-(benzo[b]thien-2-ylmethyl)-7-chloro-2,3-dihydro- (9CI) (CA INDEX NAME)



L99 ANSWER 8 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8  
 ACCESSION NUMBER: 2000:291005 HCAPLUS Full-text  
 DOCUMENT NUMBER: 132:321867  
 TITLE: Preparation of arylpyridazinones as  
 prostaglandin endoperoxide H synthase biosynthesis  
 inhibitors  
 INVENTOR(S): Black, Lawrence A.; Basha, Anwer; Kolasa, Teodozyj;  
 Kort, Michael E.; Liu, Huaqing; Mccarty, Catherine M.;  
 Patel, Meena V.; Rohde, Jeffrey J.; Coghlan, Michael  
 J.; Stewart, Andrew O.  
 PATENT ASSIGNEE(S): Abbott Laboratories, USA  
 SOURCE: PCT Int. Appl., 477 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000024719	A1	20000504	WO 1999-US25234	19991027 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2347982	A1	20000504	CA 1999-2347982	19991027 <--
AU 9965230	A1	20000515	AU 1999-65230	19991027 <--
AU 773237	B2	20040520		
EP 1124804	A1	20010822	EP 1999-953259	19991027 <--
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US 6307047	B1	20011023	US 1999-427768	19991027 <--
BR 9914858	A	20020205	BR 1999-14858	19991027 <--
JP 2003512292	T	20030402	JP 2000-578289	19991027 <--
AT 302759	T	20050915	AT 1999-953259	19991027 <--
ZA 2001003310	A	20020723	ZA 2001-3310	20010423 <--
NO 2001002061	A	20010627	NO 2001-2061	20010426 <--
NO 318623	B1	20050418		
BG 105523	A	20011231	BG 2001-105523	20010519 <--
HK 1041876	A1	20060623	HK 2002-101207	20020219 <--
PRIORITY APPLN. INFO.:			US 1998-179605	A 19981027 <--
			US 1999-261872	A 19990303 <--
			US 1999-298490	A 19990423 <--
			US 1999-427768	A 19991027 <--
			US 1997-56733P	P 19970822 <--
			US 1998-129570	B2 19980805 <--
			US 1998-137457	B2 19980820 <--
			WO 1999-US25234	W 19991027 <--
OTHER SOURCE(S): MARPAT 132:321867				
ED Entered STN: 05 May 2000				

- AB The title compds. [I; X = O, S, NR<sub>4</sub>, etc.; R<sub>4</sub> = alkyl, alkenyl, cycloalkyl, etc.; R = H, alkyl, alkenyl, etc.; at least one of R<sub>1</sub>-R<sub>3</sub> = II-III (wherein X<sub>1</sub> = SO<sub>2</sub>, SO(NR<sub>10</sub>), SO, etc.; R<sub>9</sub> = alkyl, alkenyl, alkynyl, etc.; X<sub>2</sub> = H, halo, alkyl, etc.; R<sub>10</sub> = H, alkyl, cycloalkyl); the remaining two of the groups of R<sub>1</sub>-R<sub>3</sub> = H, OH, hydroxyalkyl, etc.] which are cyclooxygenase (COX) inhibitors, and in particular, are selective inhibitors of cyclooxygenase-2 (COX-2), and therefore are useful in treating pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer, were prepared Thus, oxidation of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (preparation given) with MeCO<sub>3</sub>H in CH<sub>2</sub>Cl<sub>2</sub> afforded 86% I [X = O; R = PhCH<sub>2</sub>; R<sub>1</sub> = 4-FC<sub>6</sub>H<sub>4</sub>; R<sub>2</sub> = 4-(MeSO<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>; R<sub>3</sub> = H], which showed 0.014  $\mu$ M against COX-2. COX-2 is the inducible isoform associated with inflammation, as opposed to the constitutive isoform, cyclooxygenase-1 (COX-1) which is an important "housekeeping" enzyme in many tissues, including the gastrointestinal (GI) tract and the kidneys. The selectivity of the compds. I for COX-2 minimizes the unwanted GI and renal side-effects seen with currently marketed non-steroidal anti-inflammatory drugs (NSAIDs).
- IC ICM C07D237-14  
ICS A61K031-50; C07D405-04; C07D409-04
- CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1
- ST prostaglandin endoperoxide H synthase biosynthesis inhibitor  
arylpyridazinone prepn; arylpyridazinone prepn  
prostaglandin endoperoxide H synthase biosynthesis inhibitor;  
cyclooxygenase 2 selective inhibitor arylpyridazinone prepn;  
analgesic arylpyridazinone prepn; antipyretic  
arylpyridazinone prepn; antiinflammatory arylpyridazinone  
prepn; rheumatoid arthritis arylpyridazinone prepn;  
osteoarthritis arylpyridazinone prepn; antiarthritic  
arylpyridazinone prepn; antitumor arylpyridazinone prepn
- IT Analgesics  
Anti-inflammatory agents  
Antiarthritics  
Antipyretics  
Antitumor agents  
(preparation of arylpyridazinones as prostaglandin endoperoxide H  
synthase biosynthesis inhibitors)
- IT Osteoarthritis  
(treatment of; preparation of arylpyridazinones as prostaglandin  
endoperoxide H synthase biosynthesis inhibitors)
- IT 655-20-9P 2514-18-3P 14092-00-3P 28075-50-5P 34837-84-8P  
40400-25-7P 51437-00-4P, 1-Bromo-4-fluoro-3-methylbenzene 59982-04-6P  
63031-77-6P 84956-71-8P 89981-03-3P 97137-16-1P 98546-51-1P  
109715-47-1P 134965-39-2P 161886-22-2P, 3,4-Difluorophenylhydrazine  
213764-19-3P 221025-49-6P 221025-50-9P 221025-51-0P 221030-72-4P  
221030-73-5P 221030-74-6P 221030-75-7P 221030-76-8P 221030-77-9P  
221030-78-0P 221030-79-1P 221030-80-4P 221030-81-5P 221030-82-6P  
221030-83-7P 221030-84-8P 221030-85-9P 221030-86-0P 221030-87-1P  
221030-88-2P 221030-89-3P 221030-90-6P 221030-91-7P 221030-92-8P  
221030-93-9P 221030-94-0P 221030-95-1P 221030-96-2P 221030-97-3P  
221030-98-4P 221030-99-5P 221031-00-1P 221031-01-2P 221031-02-3P  
221031-03-4P 221031-04-5P 221031-05-6P 221031-06-7P 221031-07-8P  
221031-08-9P 221031-09-0P 221031-10-3P 221031-11-4P 221031-12-5P  
221031-13-6P 221031-14-7P 221031-15-8P 221031-16-9P 221031-17-0P  
221031-18-1P 221031-19-2P 221031-20-5P 221031-21-6P 221031-22-7P  
221031-23-8P 221031-24-9P 221031-25-0P 221031-26-1P 221031-27-2P  
221031-28-3P 221031-29-4P 221031-30-7P 221031-31-8P 221031-32-9P  
221031-33-0P 221031-34-1P 221031-35-2P 221031-36-3P 221031-37-4P  
221031-38-5P 221031-39-6P 221031-40-9P 221031-41-0P 266320-87-0P  
266320-88-1P 266320-89-2P 266320-90-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 39391-18-9, Prostaglandin endoperoxide H synthase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 109715-46-0 266320-84-7 266320-85-8 266320-86-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 221031-64-7P 221031-65-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 62-53-3, Benzenamine, reactions 65-85-0, Benzoic acid, reactions  
67-63-0, 2-Propanol, reactions 70-11-1, 2-Bromoacetophenone 71-36-3,  
n-Butanol, reactions 75-31-0, 2-Aminopropane, reactions 75-33-2,  
Isopropyl mercaptan 75-65-0, Tert-Butanol, reactions 75-66-1,  
2-Methyl-2-propanethiol 75-84-3 78-83-1, Reactions, reactions  
87-56-9, Mucochloric acid 92-66-0, 4-Bromobiphenyl 92-69-3,  
4-Phenylphenol 96-41-3, Cyclopentanol 97-95-0, 2-Ethyl-1-butanol  
98-00-0, 2-(Hydroxymethyl)furan 98-02-2, Furfuryl mercaptan 98-59-9,  
p-Toluenesulfonyl chloride 99-07-0, 3-(Dimethylamino)phenol 100-11-8  
100-39-0 100-44-7, reactions 100-51-6, Benzyl alcohol, reactions  
100-53-8, Benzyl mercaptan 101-55-3, 4-Bromodiphenylether 102-56-7,  
2,5-Dimethoxyaniline 103-63-9, (2-Bromoethyl)benzene 103-67-3,  
N-Methylbenzylamine 103-90-2 104-76-7 104-95-0, 4-Bromothioanisole  
106-37-6, 1,4-Dibromobenzene 106-38-7, 1-Bromo-4-methylbenzene  
106-39-8, 4-Bromo-1-chlorobenzene 106-41-2, p-Bromophenol 106-48-9,  
p-Chlorophenol 106-96-7, Propargyl bromide 107-18-6, 2-Propen-1-ol,  
reactions 107-82-4, 1-Bromo-3-methylbutane 108-01-0 108-11-2,  
4-Methyl-2-pentanol 108-36-1, 1,3-Dibromobenzene 108-37-2,  
1-Bromo-3-chlorobenzene 108-85-0, Cyclohexyl bromide 108-91-8,  
Cyclohexanamine, reactions 108-93-0, Cyclohexanol, reactions 108-94-1,  
Cyclohexanone, reactions 108-95-2, Phenol, reactions 109-00-2,  
3-Hydroxypyridine 109-59-1, 2-(Isopropoxy)ethanol 110-63-4,  
1,4-Butanediol, reactions 110-87-2 110-89-4, Piperidine, reactions  
110-91-8, Morpholine, reactions 116-09-6, Acetol 120-20-7,  
3,4-Dimethoxyphenethylamine 123-51-3 123-75-1, Pyrrolidine, reactions  
126-30-7 137-43-9, Cyclopentyl bromide 150-76-5, 4-Methoxyphenol  
151-18-8 156-87-6, 3-Hydroxypropylamine 339-62-8 348-57-2,  
2,4-Difluorobromobenzene 348-61-8, 1-Bromo-3,4-difluorobenzene  
349-55-3, 3-Methoxy-5-(trifluoromethyl)aniline 352-13-6,  
4-Fluorophenylmagnesium bromide 352-34-1, 4-Fluoroiodobenzene  
353-83-3, 2-Iodo-1,1,1-trifluoroethane 363-80-4, 2,3,5-Trifluoroaniline  
367-11-3, 1,2-Difluorobenzene 367-25-9, 2,4-Difluoroaniline 367-67-9,  
2-Bromo-5-nitrobenzotrifluoride 368-78-5, 3-  
(Trifluoromethyl)phenylhydrazine 371-14-2 371-40-4, 4-Fluoroaniline  
371-41-5, 4-Fluorophenol 372-19-0, 3-Fluoroaniline 372-20-3,  
3-Fluorophenol 383-53-9, 2-Bromo-4'-(trifluoromethyl)acetophenone  
395-44-8, 2-(Trifluoromethyl)benzyl bromide 401-81-0 402-43-7,  
1-Bromo-4-trifluoromethylbenzene 403-41-8, 4-Fluoro- $\alpha$ -methylbenzyl  
alcohol 405-50-5, 4-Fluorophenylacetic acid 456-41-7, 3-Fluorobenzyl  
bromide 459-46-1, 4-Fluorobenzyl bromide 460-25-3,  
1,3-Dibromo-1,1-difluoropropane 461-96-1, 3,5-Difluorobromobenzene  
488-11-9, Mucobromic acid 513-44-0, 2-Methyl-1-propanethiol 536-38-9,  
2-Bromo-4'-chloroacetophenone 541-73-1 556-96-7, 5-Bromo-m-xylene

558-43-0, 2-Methyl-1,2-propanediol 563-47-3, 3-Chloro-2-methylpropene  
 577-19-5, 1-Bromo-2-nitrobenzene 589-35-5 590-90-9,  
 4-Hydroxy-2-butanone 591-17-3, 3-Bromotoluene 600-36-2,  
 2,4-Dimethyl-3-pentanol 619-57-8, 4-Hydroxybenzamide 622-26-4,  
 4-(2-Hydroxyethyl)piperidine 622-40-2, 4-(2-Hydroxyethyl)morpholine  
 623-00-7, 4-Bromobenzonitrile 624-95-3, 3,3-Dimethyl-1-butanol  
 626-88-0, 1-Bromo-4-methylpentane 626-89-1, 4-Methyl-1-pentanol  
 627-59-8, 5-Methyl-2-hexanol 636-98-6, 1-Iodo-4-nitrobenzene 645-56-7,  
 4-(n-Propyl)phenol 661-69-8, Hexamethylditin 700-57-2, 2-Adamantanol  
 701-34-8, 4-Aminosulfonyl-1-bromobenzene 763-32-6 763-89-3 765-58-2,  
 2-Bromo-5-methylthiophene 766-00-7, Cyclopentaneethanol  
 766-02-9, 2-Cyclopentene-1-ethanol 767-00-0, 4-Cyanophenol 823-85-8,  
 4-Fluorophenylhydrazine hydrochloride 870-63-3 873-74-5,  
 4-Aminobenzonitrile 924-41-4, 1,5-Hexadien-3-ol 931-51-1,  
 Cyclohexylmagnesium chloride 1003-03-8, Cyclopentylamine 1003-09-4, 2-  
Bromothiophene 1072-85-1, 2-Fluorobromobenzene 1073-62-7,  
 Benzylhydrazine hydrochloride 1121-86-4, 1-Fluoro-3-iodobenzene  
 1126-81-4, 4-Acetamidothiophenol 1423-26-3 1462-03-9,  
 1-Methyl-1-cyclopentanol 1521-51-3, 3-Bromocyclohexene 1544-53-2  
 1569-69-3, Cyclohexyl mercaptan 1643-73-8, 4-Fluorobenzylmagnesium  
 chloride 1679-07-8, Cyclopentyl mercaptan 1679-18-1,  
 4-Chlorobenzeneboronic acid 1698-53-9, 2-Phenyl-4,5-dichloro-3(2H)-  
pyridazinone 1765-40-8, 2,3,4,5,6-Pentafluorobenzyl bromide  
 1765-93-1, 4-Fluorobenzeneboronic acid 1794-48-5 1826-67-1,  
 Vinylmagnesium bromide 1996-29-8, 1-Bromo-4-chloro-2-fluorobenzene  
 2039-86-3, 3-Bromostyrene 2076-88-2, 2-(Chloromethyl)benzo[b]  
thiophene 2081-44-9, 4-Tetrahydropyranol 2113-57-7,  
 3-Bromobiphenyl 2156-04-9 2259-30-5, Tert-Butylmagnesium bromide  
 2312-23-4, 3-Chlorophenylhydrazine hydrochloride 2357-52-0,  
 3-Fluoro-4-methoxybromobenzene 2417-72-3, Methyl 4-(bromomethyl)benzoate  
 2516-33-8, Cyclopropylmethanol 2516-34-9, Cyclobutanamine 2516-47-4,  
 Cyclopropanemethanamine 2517-43-3 2557-78-0, 2-  
Fluorothiophenol 2566-44-1, 2-(Cyclopropyl)ethanol 2567-14-8,  
 1,1,3-Trichloropropene 2568-33-4 2637-34-5, 2-Mercaptopyridine  
 2746-14-7, 1-Methylcyclopropanemethanol 2746-23-8, 3-(Chloromethyl)  
thiophene 2799-16-8 2873-18-9, 2-Bromo-5-  
chlorothiophene 2924-16-5, 3-Fluorophenylhydrazine hydrochloride  
 2938-98-9, 2-Methyl-1,4-butanediol 3179-31-5, 1H-1,2,4-Triazole-3-thiol  
 3446-89-7, 4-Methylthiobenzaldehyde 3863-11-4 3958-57-4, 3-Nitrobenzyl  
 bromide 3972-65-4, 1-Bromo-4-tert-butylbenzene 4254-29-9, 2-Indanol  
 4294-57-9, p-Tolylmagnesium bromide 4377-41-7, 2-(Chloromethyl)quinoline  
 4392-24-9, Cinnamyl bromide 4399-47-7, Cyclobutyl bromide 4548-78-1,  
 3-Methylbutylmagnesium bromide 4795-29-3, Tetrahydrofurfurylamine  
 5036-48-6, 1H-Imidazole-1-propanamine 5042-30-8, Trifluoroethylhydrazine  
 5271-38-5, 2-(Methylthio)ethanol 5332-73-0, 3-Methoxypropylamine  
 5362-55-0 5469-26-1, 1-Bromopinacolone 5673-98-3 5674-02-2,  
 Isobutylmagnesium chloride 5713-61-1, 2-Thienylmagnesium bromide  
 5720-05-8, 4-Methylphenylboronic acid 5720-06-9, 2-Methoxybenzeneboronic  
 acid 5788-58-9, 4,5-Dibromo-3(2H)-pyridazinone 6165-69-1,  
Thiophene-3-boronic acid 6351-10-6, 1-Indanol 6630-33-7,  
 2-Bromobenzaldehyde 6738-06-3, Phenylacetylenemagnesium bromide  
 6921-34-2, Benzylmagnesium chloride 7051-34-5 7342-82-7, 3-  
Bromobenzothiophene 7400-27-3, Tert-Butylhydrazine hydrochloride  
 7417-21-2, 2-(3,4-Dimethoxyphenyl)ethanol 7429-94-9 10493-44-4  
 13124-18-0, 3,4-Dichlorophenylhydrazine 13195-50-1, 2-Bromo-5-  
nitrothiophene 13291-18-4, Isopropenylmagnesium bromide  
 13331-27-6, 3-Nitrobenzeneboronic acid 14114-05-7,  
 Cyclopropyltriphenylphosphonium bromide 14282-76-9, 2-Bromo-3-  
methylthiophene 14300-71-1 14763-20-3 14763-60-1,  
 4-(Methylsulfonyl)phenol 14916-80-4, 3-Octyn-1-ol 15894-04-9

16419-60-6 16466-97-0 18729-48-1, 3-Methylcyclopentanol 19477-73-7,  
6-Bromophthalide 19614-16-5, 2-Bromothioanisole 20099-89-2,  
2-Bromo-4'-cyanoacetophenone 22037-28-1, 3-Bromofuran 22884-29-3,  
Isobutyltriphenylphosphonium bromide 23915-07-3, 2,4-Difluorobenzyl  
bromide 24070-77-7, 2-Methylcyclopentanol 26167-44-2,  
3-Chloroacetylbenzo[b]thiophene 26445-03-4, Thiocresol  
27246-81-7, 3-Bromophenylhydrazine hydrochloride 27314-17-6  
28322-40-9, Isoamyltriphenylphosphonium bromide 32916-51-1,  
Cyclopentylmagnesium chloride 33577-16-1, Methyl(methylsulfinylmethyl)su  
lfide 33598-19-5 33733-73-2, 3-Bromothioanisole 33884-43-4,  
2-(2-Bromoethyl)-1,3-dioxane 34698-41-4, 1-Indanylamine

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of arylpyridazinones as prostaglandin  
endoperoxide H synthase biosynthesis inhibitors)

IT 35166-78-0, Cyclohexylmethylmagnesium bromide 37677-17-1,  
1-Bromomethylcyclohexene 39720-27-9, 4-(Chloromethyl)phenyl acetate  
40594-37-4, 3,4-Difluorophenylhydrazine hydrochloride 40811-49-2,  
2-(Isopropylthio)ethanol 50398-79-3, 2-(Bromomethyl)-5-  
chlorothiazole 51336-94-8, 2-Chloro-2',4'-difluoroacetophenone  
51755-66-9, 3-(Methylthio)-1-hexanol 52497-07-1, 1,3-Dichloro-1-butene  
54751-01-8, 4-(Bromomethyl)pyridine 55401-97-3, 2-(Bromomethyl)pyridine  
55499-43-9 55766-17-1 56816-01-4, Ethyl (S)-3-hydroxybutanoate  
58114-09-3 59311-22-7 59311-24-9 60811-18-9, 4-Bromo-1-chloro-2-  
fluorobenzene 60811-21-4 60811-23-6, 3-Chloro-4-  
fluorothiophenol 62087-82-5, 1-Adamantyl fluoroformate  
64168-34-9, 3-Fluorobenzylmagnesium chloride 65130-46-3 69966-55-8,  
3-(Bromomethyl)pyridine 72396-61-3 72657-23-9 80657-57-4, Methyl  
(S)-3-hydroxy-2-methylpropionate 82297-89-0, 4-Fluoro-3-  
methylphenylmagnesium bromide 84282-78-0 85118-01-0,  
3,4-Difluorobenzyl bromide 85676-85-3 90555-66-1 90878-19-6,  
Phenethylmagnesium chloride 92636-36-7 93777-26-5,  
5-Bromo-2-fluorobenzaldehyde 98437-24-2, 2-Benzofuranboronic acid  
103962-10-3, 2-Bromo-4'-(trifluoromethoxy)acetophenone 112615-82-4,  
5-Methylhexylmagnesium bromide 122957-82-8 124050-15-3,  
2-(Chloromethyl)-6-fluoroquinoline 128758-41-8 128796-39-4,  
4-(Trifluoromethyl)benzeneboronic acid 134150-01-9 137504-86-0,  
3-Fluoro-4-chlorophenylboronic acid 141483-15-0, 2-Fluoro-5-  
trifluoromethylphenol 144432-85-9, 3-Chloro-4-fluorobenzeneboronic acid  
149507-26-6 151411-98-2 157911-55-2 157911-56-3 162125-08-8,  
3,4-Dichlorophenylboronic acid 162607-18-3 163105-90-6 168267-99-0  
171497-20-4 172975-69-8 175135-73-6 175135-74-7 208641-98-9  
221020-96-8 221031-42-1 221031-43-2 221031-44-3 221031-45-4  
221031-46-5 221031-47-6 221031-48-7 221031-49-8 221031-50-1  
221031-51-2 221031-52-3 221031-53-4 221031-54-5 221031-55-6  
221031-56-7 221031-57-8 221031-58-9 221031-59-0 221031-60-3  
221031-61-4 221031-62-5 221031-63-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of arylpyridazinones as prostaglandin  
endoperoxide H synthase biosynthesis inhibitors)

IT	213763-90-7P	213764-00-2P	213764-17-1P	221025-44-1P	221025-45-2P
	221025-46-3P	221025-47-4P	221025-52-1P	221025-53-2P	221025-77-0P
	221026-16-0P	221026-30-8P	221026-34-2P	221026-35-3P	221026-45-5P
	221026-46-6P	221026-51-3P	221026-61-5P	221026-62-6P	221026-78-4P
	221027-19-6P	221027-24-3P	221027-36-7P	221027-91-4P	221027-98-1P
	221028-16-6P	221028-18-8P	221028-23-5P	221028-31-5P	221028-43-9P
	221028-45-1P	221029-22-7P	221029-24-9P	221029-25-0P	221029-26-1P
	221029-28-3P	221029-32-9P	221029-41-0P	221029-43-2P	221029-46-5P
	221029-47-6P	221029-50-1P	221029-69-2P	221029-78-3P	221029-80-7P
	221029-81-8P	221029-83-0P	221029-84-1P	221029-86-3P	221030-47-3P
	221030-56-4P	221030-64-4P	221030-66-6P	221030-67-7P	266320-83-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT	213763-92-9P	213763-94-1P	213763-98-5P	213763-99-6P	213764-11-5P
	221025-48-5P	221025-54-3P	221025-55-4P	221025-56-5P	221025-57-6P
	221025-58-7P	221025-59-8P	221025-60-1P	221025-61-2P	221025-62-3P
	221025-63-4P	221025-64-5P	221025-65-6P	221025-66-7P	221025-67-8P
	221025-68-9P	221025-69-0P	221025-70-3P	221025-71-4P	221025-72-5P
	<u>221025-73-6P</u>	<u>221025-74-7P</u>	221025-75-8P	221025-76-9P	
	221025-78-1P	221025-79-2P	221025-80-5P	221025-81-6P	221025-82-7P
	221025-83-8P	221025-84-9P	221025-86-1P	221025-88-3P	221025-90-7P
	221025-92-9P	221025-94-1P	221025-96-3P	<u>221025-98-5P</u>	
	221026-00-2P	221026-02-4P	221026-04-6P	221026-05-7P	221026-06-8P
	221026-07-9P	221026-08-0P	221026-09-1P	221026-10-4P	221026-11-5P
	221026-12-6P	221026-13-7P	221026-14-8P	221026-15-9P	221026-17-1P
	221026-18-2P	221026-19-3P	221026-20-6P	221026-21-7P	221026-22-8P
	221026-23-9P	221026-24-0P	221026-25-1P	221026-26-2P	221026-27-3P
	221026-28-4P	221026-29-5P	221026-31-9P	221026-32-0P	221026-33-1P
	221026-36-4P	221026-37-5P	221026-38-6P	221026-39-7P	221026-40-0P
	221026-41-1P	221026-42-2P	221026-43-3P	221026-44-4P	221026-47-7P
	221026-48-8P	221026-49-9P	221026-50-2P	221026-52-4P	221026-53-5P
	221026-54-6P	221026-55-7P	221026-56-8P	221026-57-9P	221026-58-0P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT	266319-84-0P	266319-85-1P	266319-86-2P	266319-87-3P	266319-88-4P
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	266319-94-2P	266319-95-3P	266319-96-4P	266319-97-5P	266319-98-6P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 39391-18-9

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abbott Laboratories Usa	1999			WO 9910331 A	HCAPLUS
Abbott Laboratories Usa	1999			WO 9910332 A	HCAPLUS
Merck Frosst Canada Inc	1998			WO 9841511 A	HCAPLUS

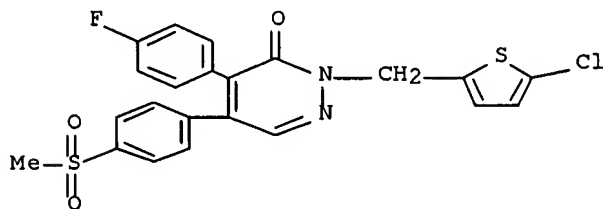
IT 221025-73-6P 221025-74-7P 221025-98-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

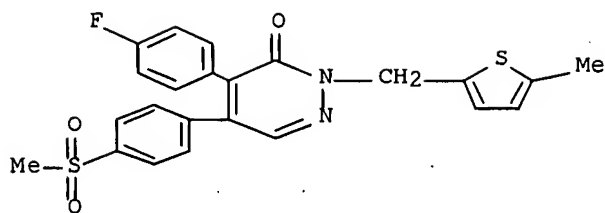
RN 221025-73-6 HCAPLUS

CN 3(2H)-Pyridazinone, 2-[(5-chloro-2-thienyl)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



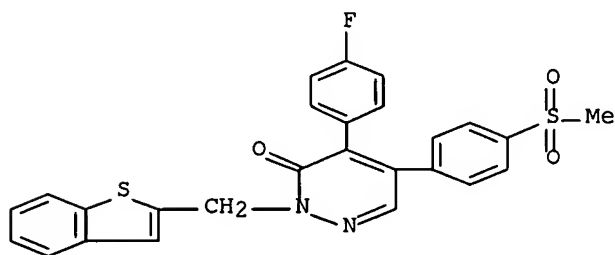
RN 221025-74-7 HCAPLUS

CN 3(2H)-Pyridazinone, 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



RN 221025-98-5 HCAPLUS

CN 3(2H)-Pyridazinone, 2-(benzo[b]thien-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 9 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9  
 ACCESSION NUMBER: 2000:161290 HCAPLUS Full-text  
 DOCUMENT NUMBER: 132:194389  
 TITLE: Preparation of thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones as immunosuppressants  
 INVENTOR(S): Bantick, John; Cooper, Martin; Perry, Matthew; Thorne, Philip  
 PATENT ASSIGNEE(S): Astra Pharmaceuticals Ltd., UK; Astra Aktiebolag  
 SOURCE: PCT Int. Appl., 99 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012514	A1	20000309	WO 1999-SE1400	19990818 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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AU 9957677	A1	20000321	AU 1999-57677	19990818 <--
AU 763758	B2	20030731		

EP 1107973	A1	20010620	EP 1999-944964	19990818 <--
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JP 2002523511	T	20020730	JP 2000-567536	19990818 <--
NZ 509809	A	20021126	NZ 1999-509809	19990818 <--
AT 253580	T	20031115	AT 1999-944964	19990818 <--
PT 1107973	T	20040331	PT 1999-944964	19990818 <--
ES 2211161	T3	20040701	ES 1999-944964	19990818 <--
US 6300334	B1	20011009	US 1999-402837	19991013 <--

PRIORITY APPLN. INFO.:

SE 1998-2895	A	19980828 <--
WO 1999-SE1400	W	19990818 <--

OTHER SOURCE(S): MARPAT 132:194389

ED Entered STN: 10 Mar 2000

AB The title compds. (I) [wherein R = C(O)Ar1 or C(R4)(R5)Ar1; R1 and R2 = independently H, (cyclo)alkyl, alkenyl, or cycloalkylmethyl; R3 = H or XR9 or XAr2; R4 = H or alkyl; R5 = H or OH; R9 = Me optionally substituted by 1 or more CN, CO2H, alkoxy, carbonyl, tetrazolyl, (un)substituted carboxyamido; R10 = H, alkyl, or R9; X = O, S(O)n, C(O)NR10, C(O)O, NHC(O)NR10, NHC(O)O, or SO2NR10; Ar1 = (un)substituted heteroaryl, Ar2 = (un)substituted Ph, pyridinyl, thienyl, pyridone, or pyridine N-oxide; n = 0-2] were prepared as immunosuppressants for the treatment of reversible obstructive airway diseases, such as asthma, bronchitis, and rhinitis. For example, II was formed in a 4-step sequence involving (1) N-addition of 1-iodo-2-methylpropane to 6-chloro-3-methyl-1H-pyrimidine-2,4-(1H,3H)-dione, (2) thiolation of the chloro compound with NaSH.H2O, (3) cycloaddn. of the 6-thioxopyrimidinedione with aqueous ClCH2CHO, and (4) coupling of the thienopyrimidinedione with 1-methylbenzimidazole-2-carboxaldehyde. In a PMA/ionomycin-stimulated peripheral blood mononuclear cell (PBMC) proliferation assay, I exhibited IA50 values of < 1  $\mu$ M.

IC ICM C07D495-04

ICS A61K031-505

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT 51-17-2, Benzimidazole 75-33-2, 1-Methylethanethiol 77-76-9, 2,2-Dimethoxypropane 81-07-2, Saccharin 85-41-6, Isoindole-1,3-dione 95-14-7, 1H-Benzotriazole 95-16-9, Benzothiazole 98-03-3, 2-Thiophenecarboxaldehyde 105-56-6, Ethyl cyanoacetate 123-75-1, Pyrrolidine, reactions 271-44-3, 1H-Indazole 271-63-6, 1H-Pyrrolo[2,3-b]pyridine 498-62-4, 3-Thiophenecarboxaldehyde 500-22-1, 3-Pyridinecarboxaldehyde 513-38-2, 1-Iodo-2-methylpropane 617-35-6, Ethyl pyruvate 872-85-5, 4-Pyridinecarboxaldehyde 1121-60-4, 2-Pyridinecarboxaldehyde 1445-69-8, Phthalhydrazide 1759-53-1, Cyclopropanecarboxylic acid 2799-21-5, (R)-3-Hydroxypyrrolidine 3012-80-4, 1-Methylbenzimidazole-2-carboxaldehyde 4318-56-3 4857-06-1, 2-Chloro-1H-benzimidazole 7051-34-5, Cyclopropylmethyl bromide 7283-96-7, 5-Chloro-2-thiophenecarboxaldehyde 7774-74-5, 2-Mercaptothiophene 10200-59-6, 2-Thiazolecarboxaldehyde 19721-22-3, 3-Mercaptopropanol 31891-06-2, 2-Amino-3-ethoxycarbonylthiophene 33821-94-2, 1-Bromo-3-(2-tetrahydropyranyl)oxypropane 36520-39-5, Azetidine hydrochloride 75860-86-5 175204-81-6, 4-Chloro-1-methyl-1H-pyrazole-3-carboxaldehyde 189278-27-1, 2-Bromo-6-trifluoromethylpyridine

RL: RCT (Reactant); RACT (Reactant or reagent)  
(reactant; preparation of thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones as immunosuppressants)

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10/518,503

259861-56-8P 259861-59-1P 259861-63-7P 259861-65-9P 259861-66-0P  
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones

as

immunosuppressants)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arzneimittelwerk Dresde	1991			DD 293824 A5	HCAPLUS
Fukumi, H	1989			JP 1213284 A	
Gutschow, M	1995	328	231	Arch Pharm (Weinheim)	MEDLINE
Takeda Chemical Industr	1995			EP 0640606 A1	HCAPLUS

IT **259861-99-9P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

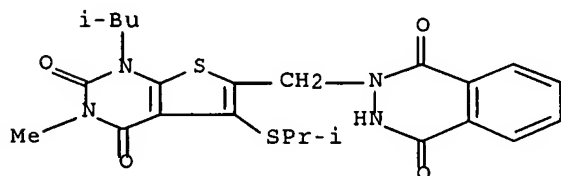
(target compound; preparation of thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones

as

immunosuppressants)

RN 259861-99-9 HCAPLUS

CN 1,4-Phthalazinedione, 2,3-dihydro-2-[[1,2,3,4-tetrahydro-3-methyl-5-[(1-methylethyl)thio]-1-(2-methylpropyl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl)methyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 10 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 1999:166604 HCAPLUS Full-text

DOCUMENT NUMBER: 130:223284

TITLE: Preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors

INVENTOR(S): Black, Lawrence A.; Basha, Anwer; Kolasa, Teodozyj; Kort, Michael E.; Liu, Huaqing; McCarty, Catherine M.; Patel, Meena V.; Rohde, Jeffrey J.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: PCT Int. Appl., 307 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910331	A1	19990304	WO 1998-US16479	19980810 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2299300	A1	19990304	CA 1998-2299300	19980810 <--
AU 9886976	A	19990316	AU 1998-86976	19980810 <--
AU 741317	B2	20011129		
EP 1007515	A1	20000614	EP 1998-938451	19980810 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
BR 9812127	A	20000718	BR 1998-12127	19980810 <--
TR 200000478	T2	20020422	TR 2000-200000478	19980810 <--
JP 2003516925	T	20030520	JP 2000-507660	19980810 <--
HU 200400909	A2	20040728	HU 2004-909	19980810 <--
IL 133552	A	20051218	IL 1998-133552	19980810 <--
ZA 9807555	A	19990223	ZA 1998-7555	19980820 <--
TW 232216	B	20050511	TW 1998-87113837	19980910 <--
NO 2000000863	A	20000222	NO 2000-863	20000222 <--
NO 315423	B1	20030901		
MX 200001850	A	20001030	MX 2000-1850	20000222 <--
BG 104241	A	20001031	BG 2000-104241	20000315 <--
BG 64675	B1	20051130		

## PRIORITY APPLN. INFO.:

US 1997-917023	A	19970822 <--
US 1998-129570	A	19980805 <--
WO 1998-US16479	W	19980810 <--

## OTHER SOURCE(S): MARPAT 130:223284

ED Entered STN: 15 Mar 1999

AB The title compds. [I; X = O, S, NR4, etc.; R4 = alkyl, alkenyl, cycloalkyl, etc.; R = H, alkyl, alkenyl, etc.; at least one of R1-R3 = II-III (wherein X1 = SO2, SO(NR10), SO, etc.; R9 = alkyl, alkenyl, alkynyl, etc.; X2 = H, halo, alkyl, etc.; R10 = H, alkyl, cycloalkyl); the remaining two of the groups of R1-R3 = H, OH, hydroxyalkyl, etc.] which are cyclooxygenase (COX) inhibitors, and in particular, are selective inhibitors of cyclooxygenase-2 (COX-2), and therefore are useful in treating pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer, were prepared. Thus, oxidation of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (preparation given) with MeCO3H in CH2Cl2 afforded 86% I [X = O; R = PhCH2; R1 = 4-FC6H4; R2 = 4-(MeSO2)C6H4; R3 = H] which showed 0.014  $\mu$ M against COX-2. COX-2 is the inducible isoform associated with inflammation, as opposed to the constitutive isoform, cyclooxygenase-1 (COX-1) which is an important "housekeeping" enzyme in many tissues, including the gastrointestinal (GI) tract and the kidneys. The selectivity of the compds. I for COX-2 minimizes the unwanted GI and renal side-effects seen with currently marketed non-steroidal anti-inflammatory drugs (NSAIDs).

IC ICM C07D237-14

ICS C07D401-06; C07D403-06; C07D237-18; C07D409-06; C07D413-06; C07D405-06; A61K031-50; C07F011-00

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1ST prostaglandin endoperoxide H synthase biosynthesis inhibitor  
arylpyridazinone prepn; arylpyridazinone prepn  
prostaglandin endoperoxide H synthase biosynthesis inhibitor;

cyclooxygenase 2 selective inhibitor arylpyridazinone prepn;  
analgesic arylpyridazinone prepn; antipyretic  
arylpyridazinone prepn; antiinflammatory arylpyridazinone  
prepn; rheumatoid arthritis arylpyridazinone prepn;  
osteoarthritis arylpyridazinone prepn; antiarthritic  
arylpyridazinone prepn; antitumor arylpyridazinone prepn

IT

Analgesics

Anti-inflammatory agents

Antiarthritics

Antipyretics

Antitumor agents

(preparation of arylpyridazinones as prostaglandin endoperoxide H  
synthase biosynthesis inhibitors)

IT

Osteoarthritis

(treatment of; preparation of arylpyridazinones as prostaglandin  
endoperoxide H synthase biosynthesis inhibitors)

IT

39391-18-9

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL  
(Biological study)

(2; preparation of arylpyridazinones as prostaglandin endoperoxide  
H synthase biosynthesis inhibitors)

IT

213763-90-7P	213764-00-2P	213764-17-1P	221025-44-1P	221025-45-2P
221025-46-3P	221025-47-4P	221025-52-1P	221025-53-2P	221025-77-0P
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221029-81-8P	221029-83-0P	221029-84-1P	221029-86-3P	221030-47-3P
221030-64-4P	221030-66-6P	221030-67-7P		

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent); USES (Uses)

(preparation of arylpyridazinones as prostaglandin endoperoxide H  
synthase biosynthesis inhibitors)

IT

213763-92-9P	213763-94-1P	213763-98-5P	213763-99-6P	213764-11-5P
221025-48-5P	221025-54-3P	221025-55-4P	221025-56-5P	221025-57-6P
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<u>221025-73-6P</u>	<u>221025-74-7P</u>	221025-75-8P	221025-76-9P	
221025-78-1P	221025-79-2P	221025-80-5P	221025-81-6P	221025-82-7P
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221025-92-9P	221025-94-1P	221025-96-3P	<u>221025-98-5P</u>	
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221028-62-2P	221028-63-3P	221028-64-4P	221028-65-5P	221028-66-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT	221028-67-7P	221028-68-8P	221028-69-9P	221028-70-2P	221028-71-3P
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 221030-71-3P 221035-92-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 39391-18-9, Prostaglandin endoperoxide H synthase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 62-53-3, Aniline, reactions 65-85-0, Benzoic acid, reactions 67-63-0, 2-Propanol, reactions 70-11-1, 2-Bromoacetophenone 75-31-0, 2-Aminopropane, reactions 75-33-2, Isopropyl mercaptan 75-65-0, tert-Butanol, reactions 75-66-1, 2-Methyl-2-propanethiol 75-84-3, 78-83-1, reactions 87-56-9, Mucochloric acid 92-66-0, 4-Bromobiphenyl 92-69-3, 4-Phenylphenol 96-41-3, Cyclopentanol 97-95-0, 2-Ethyl-1-butanol 98-00-0, 2-(Hydroxymethyl)furan 98-02-2, Furfuryl mercaptan 98-59-9, p-Toluenesulfonyl chloride 99-07-0, 3-(Dimethylamino)phenol 100-11-8 100-39-0, Benzyl bromide 100-44-7, reactions 100-51-6, Benzyl alcohol, reactions 100-53-8, Benzyl mercaptan 101-55-3, 4-Bromodiphenylether 102-56-7, 2,5-Dimethoxyaniline 103-63-9, (2-Bromoethyl)benzene 103-67-3, N-Methylbenzylamine 103-90-2, 4-Acetamidophenol 104-76-7 104-95-0, 4-Bromothioanisole 106-37-6, 1,4-Dibromobenzene 106-38-7, 1-Bromo-4-methylbenzene 106-39-8, 4-Bromo-1-chlorobenzene 106-41-2, p-Bromophenol 106-48-9, p-Chlorophenol 106-96-7, Propargyl bromide 107-18-6, 2-Propen-1-ol, reactions 107-82-4, 1-Bromo-3-methylbutane 108-01-0, N,N-(Dimethyl)ethanolamine 108-11-2, 4-Methyl-2-pentanol 108-36-1, 1,3-Dibromobenzene 108-37-2, 1-Bromo-3-chlorobenzene 108-85-0, Cyclohexyl bromide 108-91-8, Cyclohexylamine, reactions 108-93-0, Cyclohexanol, reactions 108-94-1, Cyclohexanone, reactions 108-95-2, Phenol, reactions 109-00-2, 3-Hydroxypyridine 109-59-1, 2-(Isopropoxy)ethanol 110-87-2 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 116-09-6, Acetol 120-20-7, 3,4-Dimethoxyphenethylamine 123-51-3, 3-Methyl-1-butanol 123-75-1, Pyrrolidine, reactions 137-43-9, Cyclopentyl bromide 150-76-5, 4-Methoxyphenol 151-18-8 156-87-6, 3-Hydroxypropylamine 339-62-8 348-57-2, 2,4-Difluorobromobenzene 348-61-8, 1-Bromo-3,4-difluorobenzene 349-55-3, 3-Methoxy-5-(trifluoromethyl)aniline 352-13-6, 4-Fluorophenylmagnesium bromide 352-34-1, 4-Fluoriodobenzene 353-83-3, 2-Iodo-1,1,1-trifluoroethane 363-80-4, 2,3,5-Trifluoroaniline 367-11-3, 1,2-Difluorobenzene 367-25-9, 2,4-Difluoroaniline 367-67-9, 2-Bromo-5-nitrobenzotrifluoride 371-40-4, 4-Fluoroaniline 371-41-5, 4-Fluorophenol 372-19-0, 3-Fluoroaniline 372-20-3, 3-Fluorophenol 383-53-9, 2-Bromo-4'-(trifluoromethyl)acetophenone 395-44-8, 2-(Trifluoromethyl)benzyl bromide 401-81-0 402-43-7, 1-Bromo-4-trifluoromethylbenzene 403-41-8, 4-Fluoro- $\alpha$ -methylbenzyl alcohol 405-50-5, 4-Fluorophenylacetic acid 456-41-7, 3-Fluorobenzyl bromide 459-46-1, 4-Fluorobenzyl bromide 460-25-3, 1,3-Dibromo-1,1-difluoropropane 461-96-1, 3,5-Difluorobromobenzene 488-11-9, Mucobromic acid 513-44-0, 2-Methyl-1-propanethiol 536-38-9, 2-Bromo-4'-chloroacetophenone 541-73-1 556-96-7, 5-Bromo-m-xylene 558-43-0, 2-Methyl-1,2-propanediol 563-47-3, 3-Chloro-2-methylpropene 577-19-5, 1-Bromo-2-nitrobenzene 589-35-5 590-90-9, 4-Hydroxy-2-butanone 591-17-3, 3-Bromotoluene 600-36-2, 2,4-Dimethyl-3-pentanol 619-57-8, 4-Hydroxybenzamide 622-26-4,

4-(2-Hydroxyethyl)piperidine 622-40-2, 4-(2-Hydroxyethyl)morpholine  
 623-00-7, 4-Bromobenzonitrile 624-95-3, 3,3-Dimethyl-1-butanol  
 626-88-0, 1-Bromo-4-methylpentane 626-89-1, 4-Methyl-1-pentanol  
 627-59-8, 5-Methyl-2-hexanol 636-98-6, 1-Iodo-4-nitrobenzene 645-56-7,  
 4-(n-Propyl)phenol 661-69-8, Hexamethylditin 700-57-2, 2-Adamantanol  
 701-34-8, 4-Aminosulfonyl-1-bromobenzene 763-32-6 763-89-3 765-58-2,  
 2-Bromo-5-methylthiophene 766-00-7, Cyclopentaneethanol  
 766-02-9, 2-Cyclopentene-1-ethanol 767-00-0, 4-Cyanophenol 823-85-8,  
 4-Fluorophenylhydrazine hydrochloride 870-63-3 873-74-5,  
 4-Aminobenzonitrile 924-41-4, 1,5-Hexadien-3-ol 931-51-1,  
 Cyclohexylmagnesium chloride 1003-03-8, Cyclopentylamine 1003-09-4, 2-  
Bromothiophene 1072-85-1, 2-Fluorobromobenzene 1073-62-7,  
 Benzylhydrazine hydrochloride 1121-86-4, 1-Fluoro-3-iodobenzene  
 1126-81-4, 4-Acetamidothiophenol 1423-26-3 1462-03-9,  
 1-Methyl-1-cyclopentanol 1521-51-3, 3-Bromocyclohexene 1544-53-2  
 1569-69-3, Cyclohexyl mercaptan 1643-73-8, 4-Fluorobenzylmagnesium  
 chloride 1679-07-8, Cyclopentyl mercaptan 1679-18-1,  
 4-Chlorobenzeneboronic acid 1698-53-9, 2-Phenyl-4,5-dichloro-3(2H)-  
pyridazinone 1765-40-8, 2,3,4,5,6-Pentafluorobenzyl bromide  
 1765-93-1, 4-Fluorobenzeneboronic acid 1794-48-5 1826-67-1,  
 Vinylmagnesium bromide 1996-29-8, 1-Bromo-4-chloro-2-fluorobenzene  
 2039-86-3, 3-Bromostyrene 2076-88-2, 2-(Chloromethyl)benzo[b]  
thiophene 2081-44-9, 4-Tetrahydropyranol 2113-57-7,  
 3-Bromobiphenyl 2156-04-9 2259-30-5, tert-Butylmagnesium bromide  
 2312-23-4, 3-Chlorophenylhydrazine hydrochloride 2357-52-0,  
 3-Fluoro-4-methoxybromobenzene 2417-72-3, Methyl 4-(bromomethyl)benzoate  
 2516-33-8, Cyclopropylmethanol 2516-34-9, Cyclobutylamine 2516-47-4,  
 Cyclopropylmethylamine 2517-43-3 2557-78-0, 2-Fluorothiophenol  
 2566-44-1, 2-(Cyclopropyl)ethanol 2567-14-8, 1,1,3-Trichloropropene  
 2568-33-4 2637-34-5, 2-Mercaptopyridine 2746-14-7,  
 1-Methylcyclopropanemethanol 2746-23-8, 3-(Chloromethyl)  
thiophene 2799-16-8 2873-18-9, 2-Bromo-5-  
chlorothiophene 2924-16-5, 3-Fluorophenylhydrazine hydrochloride  
 2938-98-9, 2-Methyl-1,4-butanediol 3179-31-5, 1H-1,2,4-Triazole-3-thiol  
 3446-89-7, 4-Methylthiobenzaldehyde 3958-57-4, 3-Nitrobenzyl bromide  
 3972-65-4, 1-Bromo-4-tert-butylbenzene 4254-29-9, 2-Indanol 4294-57-9,  
 p-Tolylmagnesium bromide 4377-41-7, 2-(Chloromethyl)quinoline  
 4392-24-9, Cinnamyl bromide 4399-47-7, Cyclobutyl bromide 4548-78-1,  
 3-Methylbutylmagnesium bromide 4795-29-3, Tetrahydrofurfurylamine  
 5036-48-6, 1H-Imidazole-1-propanamine 5042-30-8, Trifluoroethylhydrazine  
 5271-38-5, 2-(Methylthio)ethanol 5332-73-0, 3-Methoxypropylamine  
 5362-55-0 5469-26-1, 1-Bromopinacolone 5673-98-3 5674-02-2,  
 Isobutylmagnesium chloride 5713-61-1, 2-Thienylmagnesium bromide  
 5720-05-8, 4-Methylphenylboronic acid 5720-06-9, 2-Methoxybenzeneboronic  
 acid 5788-58-9, 4,5-Dibromo-3(2H)-pyridazinone 6165-69-1,  
Thiophene-3-boronic acid 6351-10-6, 1-Indanol 6630-33-7,  
 2-Bromobenzaldehyde 6738-06-3, Phenylacetylenemagnesium bromide  
 6921-34-2, Benzylmagnesium chloride 7051-34-5 7342-82-7, 3-  
Bromobenzothiophene 7400-27-3, tert-Butylhydrazine hydrochloride  
 7417-21-2, 2-(3,4-Dimethoxyphenyl)ethanol 7429-94-9 10493-44-4  
 13195-50-1, 2-Bromo-5-nitrothiophene 13291-18-4,  
 Isopropenylmagnesium bromide 13331-27-6, 3-Nitrobenzeneboronic acid  
 14114-05-7, Cyclopropyltriphenylphosphonium bromide 14282-76-9,  
 2-Bromo-3-methylthiophene 14300-71-1 14763-60-1,  
 4-(Methylsulfonyl)phenol 14916-80-4, 3-Octyn-1-ol 15894-04-9  
 16419-60-6 16466-97-0 18729-48-1, 3-Methylcyclopentanol 19477-73-7,  
 6-Bromophthalide 19614-16-5, 2-Bromothioanisole 20099-89-2,  
 2-Bromo-4'-cyanoacetophenone 22037-28-1, 3-Bromofuran 22884-29-3,  
 Isobutyltriphenylphosphonium bromide 23915-07-3, 2,4-Difluorobenzyl  
 bromide 24070-77-7, 2-Methylcyclopentanol 26167-44-2,

3-Chloroacetylbenzo[b]thiophene 26445-03-4, Thiocresol  
 27246-81-7, 3-Bromophenylhydrazine hydrochloride 28322-40-9,  
 Isoamyltriphenylphosphonium bromide 32916-51-1, Cyclopentylmagnesium  
 chloride 33577-16-1, Methyl(methylsulfinylmethyl)sulfide 33598-19-5  
 33733-73-2, 3-Bromothioanisole 33884-43-4, 2-(2-Bromoethyl)-1,3-dioxane  
 34698-41-4, 1-Indanylamine 35166-78-0, Cyclohexylmethylmagnesium bromide  
 37677-17-1, 1-Bromomethylcyclohexene 39720-27-9, 4-(Chloromethyl)phenyl  
 acetate 40594-37-4, 3,4-Difluorophenylhydrazine hydrochloride  
 40811-49-2, 2-(Isopropylthio)ethanol 50398-79-3, 2-(Bromomethyl)-5-  
chlorothiazole 51336-94-8, 2-Chloro-2',4'-difluoroacetophenone  
 51755-66-9, 3-(Methylthio)-1-hexanol 52497-07-1, 1,3-Dichloro-1-butene  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of arylpyridazinones as prostaglandin endoperoxide H  
 synthase biosynthesis inhibitors)

IT 54751-01-8, 4-(Bromomethyl)pyridine 55401-97-3, 2-(Bromomethyl)pyridine  
 55499-43-9 55766-17-1 58114-09-3 59311-22-7 59311-24-9  
 60811-18-9, 4-Bromo-1-chloro-2-fluorobenzene 60811-21-4 60811-23-6,  
 3-Chloro-4-fluorothiophenol 62087-82-5, 1-Adamantyl  
 fluoroformate 64168-34-9, 3-Fluorobenzylmagnesium chloride 65130-46-3  
 69966-55-8, 3-(Bromomethyl)pyridine 72657-23-9 80657-57-4, Methyl  
 (S)-3-hydroxy-2-methylpropionate 82297-89-0, 4-Fluoro-3-  
 methylphenylmagnesium bromide 85118-01-0, 3,4-Difluorobenzyl bromide  
 85676-85-3 90555-66-1 90878-19-6, Phenethylmagnesium chloride  
 92636-36-7 93777-26-5, 5-Bromo-2-fluorobenzaldehyde 98437-24-2,  
 2-Benzofuranboronic acid 103962-10-3, 2-Bromo-4'-  
 (trifluoromethoxy)acetophenone 112615-82-4, 5-Methylhexylmagnesium  
 bromide 122957-82-8 124050-15-3, 2-(Chloromethyl)-6-fluoroquinoline  
 128796-39-4, 4-(Trifluoromethyl)benzenboronic acid 134150-01-9  
 137504-86-0, 3-Fluoro-4-chlorophenylboronic acid 141483-15-0,  
 2-Fluoro-5-trifluoromethylphenol 144432-85-9, 3-Chloro-4-  
 fluorobenzeneboronic acid 149507-26-6 151411-98-2 157911-55-2  
 157911-56-3 162125-08-8, 3,4-Dichlorophenylboronic acid 162607-18-3  
 163105-90-6 168267-99-0 171497-20-4 172975-69-8 175135-73-6  
 175135-74-7 208641-98-9 221020-96-8 221031-42-1 221031-43-2  
 221031-44-3 221031-45-4 221031-46-5 221031-47-6 221031-48-7  
 221031-49-8 221031-50-1 221031-51-2 221031-52-3 221031-53-4  
 221031-54-5 221031-55-6 221031-56-7 221031-57-8 221031-58-9  
 221031-59-0 221031-60-3 221031-61-4 221031-62-5 221031-63-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of arylpyridazinones as prostaglandin endoperoxide H  
 synthase biosynthesis inhibitors)

IT 655-20-9P 2514-18-3P 14092-00-3P 28075-50-5P 34837-84-8P  
 40400-25-7P 51437-00-4P, 1-Bromo-4-fluoro-3-methylbenzene 59982-04-6P  
 63031-77-6P 84956-71-8P 89981-03-3P 97137-16-1P 98546-51-1P  
 134965-39-2P 213764-19-3P 221025-49-6P 221025-50-9P 221025-51-0P  
 221030-72-4P 221030-73-5P 221030-74-6P 221030-75-7P 221030-76-8P  
 221030-77-9P 221030-78-0P 221030-79-1P 221030-80-4P 221030-81-5P  
 221030-82-6P 221030-83-7P 221030-84-8P 221030-85-9P 221030-86-0P  
 221030-87-1P 221030-88-2P 221030-89-3P 221030-90-6P 221030-91-7P  
 221030-92-8P 221030-93-9P 221030-94-0P 221030-95-1P 221030-96-2P  
 221030-97-3P 221030-98-4P 221030-99-5P 221031-00-1P 221031-01-2P  
 221031-02-3P 221031-03-4P 221031-04-5P 221031-05-6P 221031-06-7P  
 221031-07-8P 221031-08-9P 221031-09-0P 221031-10-3P 221031-11-4P  
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 221031-17-0P 221031-18-1P 221031-19-2P 221031-20-5P 221031-21-6P  
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 221031-37-4P 221031-38-5P 221031-39-6P 221031-40-9P 221031-41-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 221031-64-7P 221031-65-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
F Hoffmann-La Roche Ag	1996			EP 0714895 A	HCAPLUS
Griswold, D	1996	16	181	MEDICINAL RESEARCH R	HCAPLUS
Medicis Corporation	1988			WO 8809675 A	HCAPLUS
Rohm And Haas Company	1996			EP 0711759 A	HCAPLUS

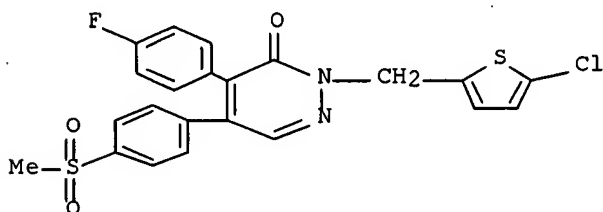
IT 221025-73-6P 221025-74-7P 221025-98-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

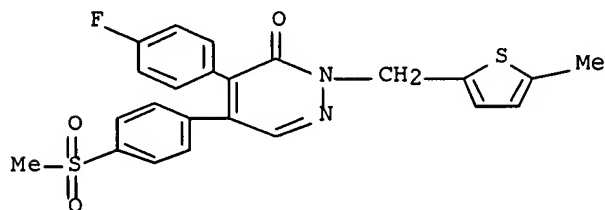
RN 221025-73-6 HCAPLUS

CN 3(2H)-Pyridazinone, 2-[(5-chloro-2-thienyl)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



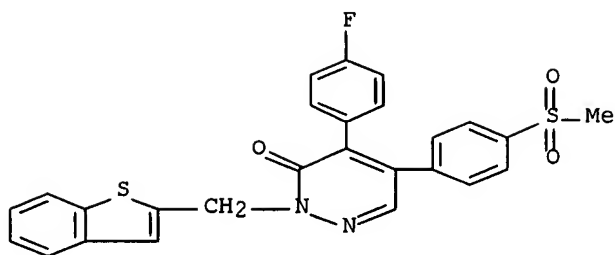
RN 221025-74-7 HCAPLUS

CN 3(2H)-Pyridazinone, 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



RN 221025-98-5 HCAPLUS

CN 3(2H)-Pyridazinone, 2-(benzo[b]thien-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 11 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 1994:435618 HCAPLUS Full-text

DOCUMENT NUMBER: 121:35618

TITLE: Pyridazinone derivatives and processes for preparing them

INVENTOR(S): Ishida, Akihiko; Homma, Koichi; Kono, Harumichi; Tamura, Koji; Sasaki, Yasuhiko

PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 47 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 579059	A1	19940119	EP 1993-110611	19930702 <--
EP 579059	B1	19990512		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 06016663	A	19940125	JP 1992-215354	19920702 <--
CA 2099743	A1	19940103	CA 1993-2099743	19930629 <--
JP 06073020	A	19940315	JP 1993-159338	19930629 <--
AT 179972	T	19990515	AT 1993-110611	19930702 <--
US 5739132	A	19980414	US 1996-767444	19961216 <--
PRIORITY APPLN. INFO.:			JP 1992-215354	A 19920702 <--
			JP 1992-215355	A 19920702 <--
			US 1993-83489	B1 19930630 <--

OTHER SOURCE(S): MARPAT 121:35618

ED Entered STN: 23 Jul 1994

AB Pyridazinones I wherein (1) R<sub>1</sub> is a substituted or unsubstituted C<sub>1</sub>-10 alkyl, a C<sub>3</sub>-6 cycloalkyl, a lower alkenyl, a heterocyclic group having N, O or S atom or camphor-10-yl; R<sub>3</sub> is hydrogen, a substituted or unsubstituted lower alkyl or a lower alkenyl; or R<sub>1</sub> and R<sub>3</sub> are bonded at terminal ends thereof to form a lower alkylene; and Z is a group represented by II where n is 1 or 2; and D is hydrogen or a halogen; or (2) R<sub>1</sub> is a substituted or unsubstituted C<sub>1</sub>-10 alkyl, a substituted or unsubstituted Ph, a C<sub>3</sub>-6 cycloalkyl, a lower alkenyl, a heterocyclic group having N, O or S atom or camphor-10-yl; R<sub>3</sub> is hydrogen, a substituted or unsubstituted lower alkyl or a lower alkenyl; or R<sub>1</sub> and R<sub>3</sub> are bonded at terminal ends thereof to form a lower alkylene; and Z is a group represented by III and R<sub>2</sub> is hydrogen, a substituted or unsubstituted lower alkyl, an aryl or a lower alkenyl; and -A-B- is an ethylene or vinylene each of which may be substituted by 1 or 2 groups selected from the group consisting of a lower alkyl and Ph group, or a pharmaceutically acceptable salt thereof were prepared and are useful for protecting from endotoxin shock and curing nephritis. Thus, mice treated with 2-methylsulfonylamino-5-[4,5-

dihydropyridazin -3(2H)-on-6-yl]indan (prepared by methanesulfonylation of 2-amino-5-[4,5- dihydropyridazin-3(2H)-on-6-yl]indan) had 100% survival rate vs. a control when infected with an endotoxin (lipopolysaccharide) derived from *Escherichia coli*.

IC ICM C07D237-04  
ICS C07D237-14; C07D409-04; A61K031-50; C07D401-12; C07D409-12;  
C07D413-12; C07D417-12; C07D403-12; C07D409-06; C07D401-06;  
C07D403-06; C07D401-14  
CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1  
ST pyridazinone prepn endotoxin shock nephritis  
IT Shock  
(endotoxin, pyridazinones for)  
IT Kidney, disease  
(nephritis, pyridazinones for treatment of)  
IT 31952-21-3P 82985-09-9P 138993-85-8P 155719-25-8P 155719-31-6P  
155719-32-7P 155719-33-8P 155719-35-0P 155719-36-1P 155719-37-2P  
155719-41-8P 155719-43-0P 155719-50-9P 155719-51-0P 155719-52-1P  
155719-53-2P 155719-54-3P 155719-60-1P 155719-62-3P 155719-63-4P  
155719-64-5P 155719-66-7P 155719-67-8P 155719-68-9P 155719-69-0P  
155719-70-3P 155719-71-4P 155719-72-5P 155719-73-6P 155719-74-7P  
155719-75-8P 155719-76-9P 155719-77-0P 155719-78-1P 155719-79-2P  
155719-80-5P 166978-75-2P 166978-76-3P 166978-77-4P 166978-78-5P  
166978-85-4P 172680-14-7P 172680-41-0P 172680-79-4P 172680-80-7P  
172680-81-8P 172680-82-9P 172680-83-0P 172680-85-2P 172680-87-4P  
172680-88-5P 172680-89-6P 172680-90-9P 172680-91-0P 172680-92-1P  
172680-93-2P 172680-94-3P 172680-99-8P 172681-00-4P 172681-01-5P  
172681-02-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and reaction of, in preparation of pyridazinones for endotoxin shock protection and nephritis treatment)

IT 155718-08-4P 155718-23-3P 155718-25-5P 155718-27-7P 155718-33-5P  
155718-34-6P 155718-38-0P 155718-49-3P 155718-66-4P 155718-74-4P  
155718-80-2P 155718-89-1P 155718-90-4P 155718-92-6P 155719-08-7P  
155719-09-8P 155719-10-1P 155719-11-2P 155719-12-3P 155719-13-4P  
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155719-19-0P 155719-20-3P 155719-21-4P 155719-22-5P 155719-23-6P  
172679-62-8P 172679-63-9P 172679-64-0P 172679-65-1P 172679-66-2P  
172679-67-3P 172679-68-4P 172679-69-5P 172679-70-8P 172679-71-9P  
172679-72-0P 172679-73-1P 172679-74-2P 172679-75-3P 172679-76-4P  
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172679-82-2P 172679-83-3P 172679-84-4P 172679-85-5P 172679-86-6P  
172679-88-8P 172679-92-4P 172679-93-5P 172679-94-6P 172679-95-7P  
172679-96-8P 172679-97-9P 172680-00-1P 172680-01-2P 172680-02-3P  
172680-03-4P 172680-04-5P 172680-05-6P 172680-06-7P 172680-07-8P  
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172680-16-9P 172680-17-0P 172680-18-1P 172680-19-2P 172680-20-5P  
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172680-38-5P 172680-39-6P 172680-40-9P 172680-42-1P 172680-43-2P  
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172680-56-7P 172680-57-8P 172680-58-9P 172680-59-0P 172680-60-3P  
172680-61-4P 172680-62-5P 172680-63-6P 172680-64-7P 172680-65-8P  
172680-66-9P 172680-67-0P 172680-68-1P 172680-69-2P 172680-70-5P  
172680-89-6P 172680-90-9P 172680-91-0P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, for endotoxin shock protection and nephritis treatment)

IT 75-36-5, Acetyl chloride 75-77-4, Chlorotrimethylsilane, reactions  
 75-86-5 79-22-1, Methyl chlorocarbonate 79-30-1, 2-Methylpropionyl  
 chloride 85-44-9, 1,3-Isobenzofurandione 98-09-9, Benzenesulfonyl  
 chloride 100-39-0, Benzyl bromide 100-52-7, Benzaldehyde, reactions  
 103-80-0, Phenylacetyl chloride 105-36-2, Ethyl bromoacetate 107-08-4,  
 Propyl iodide 108-30-5, reactions 124-63-0, Methanesulfonyl chloride  
 127-68-4 302-01-2, Hydrazine, reactions 407-25-0, Trifluoroacetic  
 anhydride 617-86-7, Triethylsilane 754-03-0, Ethanesulfonyl fluoride  
 1490-25-1 1622-32-8 1633-82-5 2386-60-9, Butanesulfonyl chloride  
 2975-41-9, 2-Aminoindan 3099-31-8, 3-Picolyl chloride 3144-16-9,  
 (+)-Camphorsulfonic acid 3878-55-5, Methyl hydrogen succinate  
 4584-46-7 16029-98-4 16629-19-9, 2-Thiophenesulfonyl  
 chloride 114149-01-8 138006-38-9 155718-74-4 155719-08-7  
 155719-63-4 155719-80-5 155719-82-7 155719-85-0 155719-86-1  
 166978-75-2 172679-98-0 172680-34-1 172680-55-6 172680-56-7  
 172680-84-1 172680-86-3

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, in preparation of pyridazinones for endotoxin shock  
 protection and nephritis treatment)

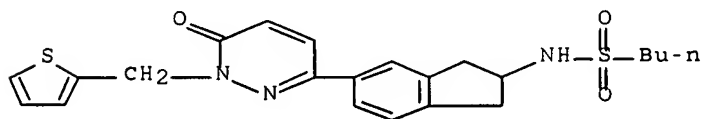
IT 172680-47-6P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, for endotoxin shock protection and nephritis treatment)

RN 172680-47-6 HCAPLUS

CN 1-Butanesulfonamide, N-[5-[1,6-dihydro-6-oxo-1-(2-thienylmethyl)-3-  
 pyridazinyl]-2,3-dihydro-1H-inden-2-yl]- (9CI) (CA INDEX NAME)



L99 ANSWER 12 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 1994:134401 HCAPLUS Full-text

DOCUMENT NUMBER: 120:134401

TITLE: Novel antiasthmatic agents with dual activities of  
 thromboxane A2 synthetase inhibition and  
 bronchodilation. 2. 4-(3-Pyridyl)-1(2H)-phthalazinones

AUTHOR(S): Yamaguchi, Masahisa; Kamei, Kenshi; Koga, Takaki;  
 Akima, Michitaka; Maruyama, Akinori; Kuroki, Toshio;  
 Ohi, Nobuhiro

CORPORATE SOURCE: Fuji-Gotemba Res. Lab., Chugai Pharm. Co., Ltd.,  
 Gotemba, 412, Japan

SOURCE: Journal of Medicinal Chemistry (1993),  
 36(25), 4061-8  
 CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal  
 LANGUAGE: English

ED Entered STN: 19 Mar 1994

AB A series of novel 4-(3-pyridyl)-1(2H)-phthalazinone derivs. which possess dual  
 activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodilation  
 was synthesized, and their pharmacol. activities were evaluated. While the  
 length and the bulk of 2-alkyl substituents had no influence on either  
 activity, the 2-substituents with polar groups reduced bronchodilatory  
 activity. On introduction of heteroarom. nuclei into the 4-position of the  
 phthalazinone I (R = 1-imidazolyl, R1 = Et) and I (R = 5-thiazolyl, R1 = Me,

Et) were as active as the parent I (R = 3-pyridyl, R1 = Et). These findings suggest that heteroarom. nuclei at the 4-position of phthalazinones play a critical role in TXA2 synthetase inhibition. Addnl., the hydrophobicity of the compds. was found to exert a marked influence on bronchodilatory activity. These observations led to the selection of 2-ethyl-4-(3-pyridyl)-1(2H)-phthalazinone (I, R = 3-pyridyl, R1 = Et) (KK-505) and 2-methyl-4-(5-thiazolyl)-1(2H)-phthalazinone (I, R = 5-thiazolyl, R1 = Me,) (KK-562) for further studies. Although their precise mechanism of action remains unclear, this series of novel phthalazinone derivs. represents a new class of antiasthma agents with dual activities.

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 7

IT 75884-68-3P 137381-08-9P 137381-66-9P 137381-67-0P 137381-68-1P  
 137381-69-2P 137381-70-5P 137381-71-6P 137381-72-7P 137381-74-9P  
 137381-75-0P 137381-77-2P 137381-78-3P 137381-79-4P 137381-80-7P  
 137381-81-8P 137381-82-9P 137381-85-2P 137381-86-3P 137381-87-4P  
 137381-89-6P 137381-90-9P 137381-91-0P 137381-92-1P 137381-94-3P  
 137381-95-4P 137381-96-5P 137381-98-7P 137382-00-4P  
137382-01-5P 137382-02-6P 137382-04-8P 137382-05-9P  
 137382-06-0P 137382-07-1P 137382-08-2P 137382-10-6P 137382-11-7P  
 137382-12-8P 137382-13-9P 137382-14-0P 137382-15-1P 137382-16-2P  
 137382-18-4P 137382-36-6P 153077-98-6P 153077-99-7P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation and thromboxane A2 synthetase inhibition and bronchodilation activity of)

IT 108-98-5, Benzenethiol, reactions 288-94-8, 1H-Tetrazole 1450-85-7,  
 2-Pyrimidinethiol 25377-76-8, 2-Thiazolinethiol

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, with (bromoethyl)phthalazinones)

IT 288-47-1, Thiazole 4595-59-9, 5-Bromopyrimidine 79265-30-8,  
 2-(Trimethylsilyl)thiazole

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, with phthalic anhydride)

IT 85-44-9, Phthalic anhydride

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, with thiazole)

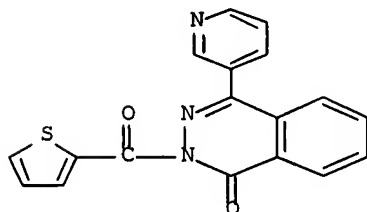
IT 137382-01-5P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation and thromboxane A2 synthetase inhibition and bronchodilation activity of)

RN 137382-01-5 HCAPLUS

CN 1(2H)-Phthalazinone, 4-(3-pyridinyl)-2-(2-thienylcarbonyl)- (9CI) (CA  
 INDEX NAME)



ACCESSION NUMBER: 1992:83619 HCAPLUS Full-text  
DOCUMENT NUMBER: 116:83619  
TITLE: Potent, orally active aldose reductase inhibitors  
related to zopolrestat: surrogates for  
benzothiazole side chain  
AUTHOR(S): Mylari, Banavara L.; Beyer, Thomas A.; Scott, Pamela  
J.; Aldinger, Charles E.; Dee, Michael F.; Siegel,  
Todd W.; Zembrowski, William J.  
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA  
SOURCE: Journal of Medicinal Chemistry (1992),  
35(3), 457-65  
CODEN: JMCMAR; ISSN: 0022-2623  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ED Entered STN: 06 Mar 1992

AB A broad structure-activity program was undertaken in search of effective surrogates for the key benzothiazole side chain of the potent aldose reductase inhibitor, zopolrestat. A structure-driven approach was pursued, which spanned exploration of three areas: (1) 5/6 fused heterocycles, such as benzoxazole, benzothiophene, benzofuran, and imidazopyridine; (2) 5-membered heterocycles, including oxadiazole, oxazole, thiazole, and thiadiazole, with pendant aryl groups, and (3) thioanilide as a formal equivalent of benzothiazole. Several benzoxazole- and 1,2,4-oxadiazole-derived analogs were found to be potent inhibitors of aldose reductase from human placenta and were orally active in preventing sorbitol accumulation in rat sciatic nerve, in an acute test of diabetic complications. Phthalazineacetic acid I was the best of the benzoxazole series ( $IC_{50} = 3.2 \times 10^{-9}M$ ); it suppressed accumulation of sorbitol in rat sciatic nerve by 78% at an oral dose of 10 mg/kg. Oxadiazolyl derivative II with  $IC_{50} < 1.0 \times 10^{-8}M$ , caused a 69% reduction in sorbitol accumulation in rat sciatic nerve at an oral dose of 25 mg/kg. The thioanilide side chain features in III proved to be an effective surrogate for benzothiazole. III was highly potent in vitro ( $IC_{50} = 5.2 \times 10^{-8}M$ ) but did not show oral activity when tested at 100 mg/kg. Addnl. structure-activity relationships encompassing a variety of heterocyclic side chains are discussed.

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

IT	110703-54-3P	110703-55-4P	110703-57-6P	110703-59-8P	110703-60-1P
	110703-62-3P	110703-63-4P	110703-64-5P	110703-73-6P	110703-74-7P
	110703-77-0P	<u>110703-78-1P</u>	110721-48-7P	110722-35-5P	
	110722-36-6P	110722-45-7P	110722-46-8P	110749-07-0P	110749-08-1P
	112065-65-3P	<u>124168-21-4P</u>	131337-23-0P	131337-24-1P	
	131337-27-4P	131337-28-5P	131337-29-6P	131337-32-1P	131337-33-2P
	<u>131337-35-4P</u>	<u>131337-37-6P</u>	<u>131337-38-7P</u>		
	138129-12-1P	138129-13-2P	138129-14-3P	138129-29-0P	138129-30-3P
	138129-31-4P	138129-32-5P	138129-33-6P	138129-34-7P	138129-35-8P
	138129-36-9P	138129-37-0P	138129-38-1P	138129-39-2P	138129-40-5P
	138129-41-6P	138129-42-7P	138129-43-8P	138129-44-9P	138151-14-1P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and aldose reductase inhibition of)

IT	110703-66-7P	110703-79-2P	110703-80-5P	110703-81-6P	110703-83-8P
	110703-87-2P	110703-88-3P	110703-91-8P	<u>110703-92-9P</u>	
	110704-53-5P	110704-54-6P	110722-33-3P	110722-34-4P	110722-37-7P
	110722-38-8P	110722-39-9P	110722-41-3P	110722-43-5P	110722-44-6P
	110749-09-2P	<u>124168-24-7P</u>	131337-22-9P	131337-26-3P	
	<u>131337-39-8P</u>	<u>131337-40-1P</u>	131337-42-3P	131337-45-6P	
	131337-46-7P	<u>131337-48-9P</u>	131337-54-7P	138128-87-7P	
	138128-88-8P	138128-89-9P	138128-91-3P	138128-92-4P	138128-93-5P
	138128-94-6P	<u>138128-95-7P</u>	<u>138128-96-8P</u>	138128-97-9P	
	138128-98-0P	138128-99-1P	138129-00-7P	138129-01-8P	138129-02-9P

10/518,503

138129-03-0P 138129-04-1P 138129-05-2P 138129-06-3P 138129-07-4P  
138129-08-5P 138129-09-6P 138129-10-9P 138129-11-0P 138129-15-4P  
138129-16-5P 138129-17-6P 138129-18-7P 138129-19-8P 138129-21-2P  
138129-22-3P 138129-23-4P 138129-24-5P 138129-25-6P 138129-26-7P  
138129-27-8P 138129-28-9P 138151-13-0P

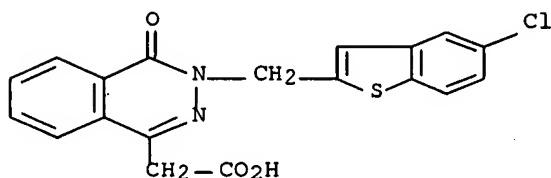
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of)

IT 110703-78-1P 124168-21-4P 131337-35-4P  
131337-37-6P 131337-38-7P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and aldose reductase inhibition of)

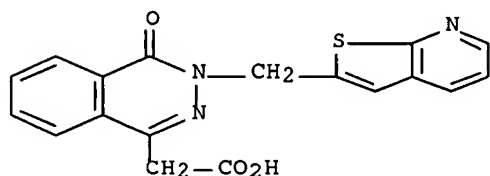
RN 110703-78-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



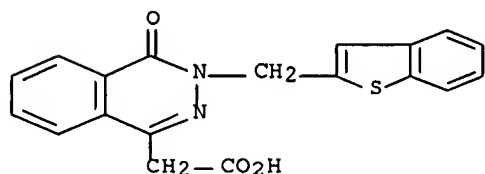
RN 124168-21-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-ylmethyl)- (9CI) (CA INDEX NAME)



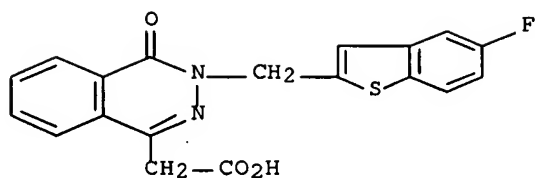
RN 131337-35-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3-(benzo[b]thien-2-ylmethyl)-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



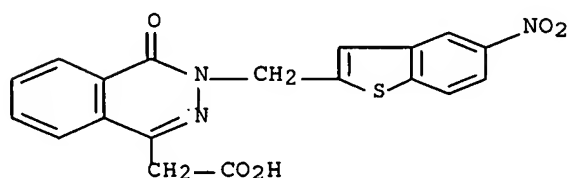
RN 131337-37-6 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-fluorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



RN 131337-38-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(5-nitrobenzo[b]thien-2-yl)methyl]-4-oxo- (9CI) (CA INDEX NAME)

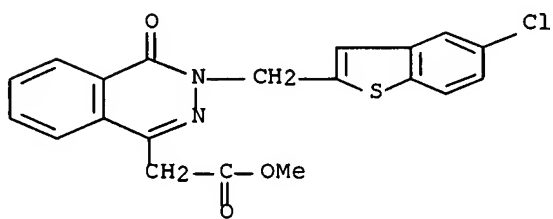


IT 110703-92-9P 124168-24-7P 131337-39-8P  
131337-40-1P 131337-48-9P 138128-95-7P  
138128-96-8P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)

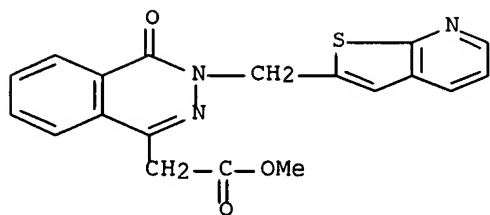
RN 110703-92-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



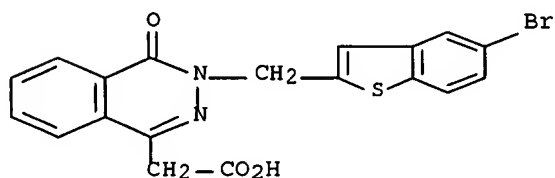
RN 124168-24-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-ylmethyl)-, methyl ester (9CI) (CA INDEX NAME)



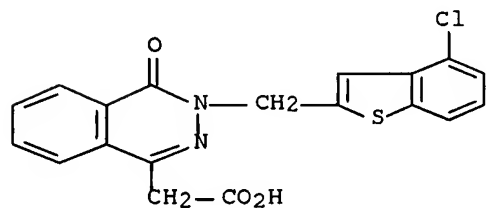
RN 131337-39-8 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-bromobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



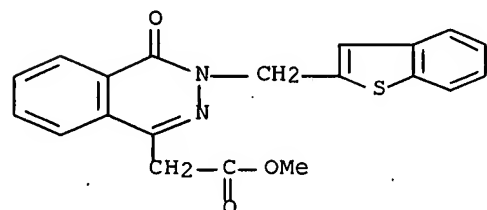
RN 131337-40-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(4-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



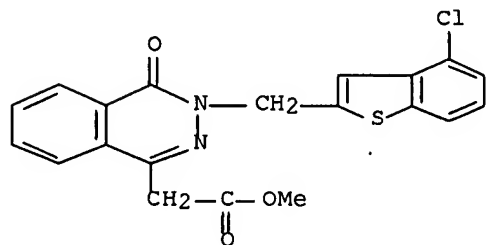
RN 131337-48-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-(benzo[b]thien-2-ylmethyl)-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



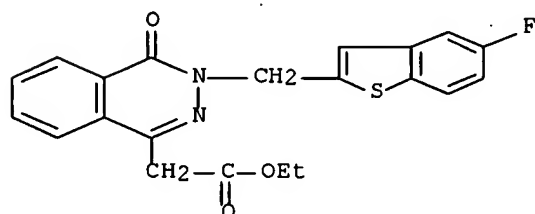
RN 138128-95-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(4-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



RN 138128-96-8 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-fluorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



L99 ANSWER 14 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:205961 HCAPLUS Full-text

DOCUMENT NUMBER: 142:197900

TITLE: Product class 10: phthalazines

AUTHOR(S): Haider, N.; Holzer, W.

CORPORATE SOURCE: Germany

SOURCE: Science of Synthesis (2004), 16, 315-372

CODEN: SSCYJ9

PUBLISHER: Georg Thieme Verlag

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 15 Mar 2004

AB A review. Preparation is given for phthalazines via ring closure or transformation reactions, aromatization or substituent modification.

CC 28-0 (Heterocyclic Compounds (More Than One Hetero Atom))

IT 50-00-0, Formaldehyde, reactions 57-13-6, Urea, reactions 57-56-7, Hydrazinecarboxamide 60-34-4 62-53-3, Benzenamine, reactions 64-19-7, Acetic acid, reactions 67-62-9 70-11-1 71-43-2, Benzene, reactions 74-89-5, Methanamine, reactions 75-07-0, Acetaldehyde, reactions 75-16-1 75-24-1 77-78-1 79-19-6, Hydrazinecarbothioamide 79-22-1 84-58-2 85-44-9, 1,3-Isobenzofurandione 85-52-9 88-99-3, 1,2-Benzenedicarboxylic acid, reactions 89-74-7 91-15-6, 1,2-Benzenedicarbonitrile 93-60-7 93-98-1 95-47-6, reactions 95-76-1 98-01-1, 2-Furancarboxaldehyde, reactions 98-03-3, 2-Thiophenecarboxaldehyde 98-09-9, Benzenesulfonyl chloride

98-80-6 98-88-4, Benzoyl chloride 100-44-7, reactions 100-52-7,  
 Benzaldehyde, reactions 100-61-8, reactions 100-63-0 104-87-0  
 104-88-1, reactions 105-36-2 105-39-5 105-53-3 105-56-6  
 106-42-3, reactions 106-47-8, reactions 107-13-1, 2-Propenenitrile,  
 reactions 107-14-2 108-24-7 108-38-3, reactions 108-88-3,  
 reactions 108-95-2, Phenol, reactions 109-01-3 109-65-9 109-72-8,  
 reactions 109-73-9, 1-Butanamine, reactions 109-77-3, Propanedinitrile  
 109-84-2 110-18-9 110-46-3 113-00-8, Guanidine 118-92-3 119-67-5  
 120-14-9 120-57-0, 1,3-Benzodioxole-5-carboxaldehyde 121-69-7,  
 reactions 123-11-5, reactions 123-75-1, Pyrrolidine, reactions  
 128-08-5 140-29-4, Benzeneacetoneitrile 141-43-5, reactions 334-88-3  
 368-39-8 368-78-5 420-04-2, Cyanamide 462-80-6, 1,3-Cyclohexadien-5-  
 yne 479-87-8 480-91-1 536-40-3 555-96-4 577-56-0 589-21-9  
 591-50-4 603-11-2 610-93-5 613-94-5 623-73-4 637-80-9 641-63-4  
 642-27-3 643-79-8, 1,2-Benzenedicarboxaldehyde 652-40-4 670-80-4  
 704-00-7 762-42-5 824-79-3 865-47-4 917-54-4 936-52-7 942-81-4  
 1122-91-4 1125-99-1 1129-28-8 1159-86-0 1530-45-6 1576-35-8  
 1673-47-8 1679-18-1 1766-63-8 1875-48-5 1885-14-9 1997-41-7  
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 2360-45-4 2368-80-1 2417-72-3 2417-73-4 2435-53-2 2459-07-6  
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 [1,1'-Biphenyl]-3,4-dicarboxylic acid 4521-61-3 4540-16-3 4821-94-7  
 4870-65-9 5004-42-2 5271-67-0, 2-Thiophenecarbonyl chloride  
 5720-05-8 5720-06-9 5720-07-0 5814-05-1 5999-20-2 6118-66-7  
 6781-29-9 6830-78-0 6833-23-4 7087-68-5 7112-37-0 7148-07-4  
 7464-91-7 7465-88-5 7477-28-3 7658-80-2 7677-24-9 7681-11-0,  
 Potassium iodide (KI), reactions 7694-81-7, 1-Phthalazinecarbonitrile  
 10034-85-2, Hydriodic acid 10251-20-4 10365-98-7 10478-89-4  
 10478-99-6 13050-47-0 13209-15-9 13746-66-2 14092-11-6  
 14352-51-3 14660-52-7 14671-41-1 15994-77-1 16675-55-1  
 16721-80-5, Sodium sulfide (Na(SH)) 17082-09-6 17127-13-8 17933-03-8  
 18138-18-6 18496-19-0 18584-63-9 19064-68-7 19172-47-5  
 19641-29-3 20277-69-4 21343-93-1 21950-75-4 22446-12-4  
 23952-05-8 24280-34-0 24826-74-2 25641-99-0 25732-35-8  
 27693-49-8 29360-77-8 32003-14-8 33027-12-2 33133-69-6  
 33901-44-9 33901-46-1 34613-09-7 37074-38-7 39519-78-3  
 39830-63-2 42760-46-3 42833-31-8 43073-12-7 43111-31-5  
 43111-32-6 46496-80-4 50635-21-7 50635-22-8 50635-23-9  
 52010-22-7 52044-75-4 52302-45-1, 1,3-Benzodioxole-5,6-  
 dicarboxaldehyde 54109-03-4 56107-12-1 56107-13-2 56611-61-1  
 57901-54-9 58268-28-3 61503-68-2 63503-60-6 63536-24-3  
 63536-25-4 63536-26-5 63536-27-6 63536-28-7 64019-77-8  
 64779-60-8 65095-33-2 65237-17-4 65489-47-6 66645-91-8

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of phthalazines)

IT 86-54-4P 269-50-1P, 1,3-Dioxolo[4,5-g]phthalazine 1133-73-9P  
 2258-88-0P 3306-76-1P 3682-15-3P 4776-85-6P 4870-16-0P  
 5439-98-5P 5441-28-1P 6091-81-2P 6266-49-5P 6941-96-4P  
 7188-22-9P 10089-99-3P 10132-02-2P 10132-05-5P 13580-85-3P  
 13580-86-4P 13580-88-6P 13705-95-8P 14062-52-3P 14161-35-4P  
 16676-79-2P 17045-94-2P 17045-95-3P 18393-54-9P 18496-20-3P  
 18584-50-4P 18584-52-6P 18584-53-7P 18584-54-8P 18636-89-0P  
 18640-46-5P 18697-31-9P 21948-84-5P 23100-01-8P 24129-03-1P  
 24129-10-0P 24953-61-5P 24953-63-7P 24953-64-8P 24953-65-9P  
 25131-53-7P 25732-39-2P 25732-41-6P 25732-42-7P 26238-15-3P  
 26641-43-0P 28081-56-3P 29415-71-2P 29902-28-1P 36503-83-0P  
 38933-79-8P 39794-28-0P 39794-29-1P 39998-72-6P 41886-43-5P  
 49572-99-8P 51334-85-1P 51935-42-3P 54145-30-1P 57413-62-4P

57835-94-6P 59283-65-7P 59908-32-6P 60889-20-5P 61503-69-3P  
62645-07-2P 63536-23-2P 63536-29-8P 63536-30-1P 63536-31-2P  
63536-36-7P 66859-14-1P 68775-90-6P 68775-92-8P 71271-35-7P  
73662-08-5P 73662-09-6P 73662-10-9P 76240-45-4P 76240-46-5P  
76240-47-6P 76462-35-6P 76462-36-7P 76870-65-0P 76972-37-7P  
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87166-61-8P 87255-77-4P 89898-93-1P 89898-94-2P 89898-95-3P  
89939-65-1P 90876-71-4P 93517-74-9P 93517-75-0P 93517-76-1P  
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RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of phthalazines)

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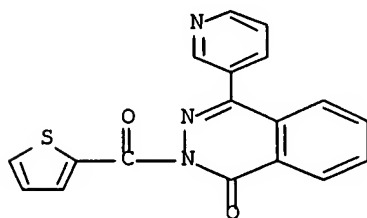
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Togo, H	1991	32	6559	Tetrahedron Lett	HCAPLUS
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Zugravescu, I	1962	7	1405	Rev Chim, Acad Rep P	HCAPLUS

IT **137382-01-5P**RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of phthalazines)

RN 137382-01-5 HCAPLUS

CN 1(2H)-Phthalazinone, 4-(3-pyridinyl)-2-(2-thienylcarbonyl)- (9CI) (CA  
INDEX NAME)

L99 ANSWER 15 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:489233 HCAPLUS Full-text

DOCUMENT NUMBER: 135:92640

TITLE: Preparation of 1,2,5,10-tetrahydropyridazino  
[4,5-b]quinoline-1,10-diones for the treatment of painINVENTOR(S): Brown, Dean Gordon; Bare, Thomas Michael; Murphy,  
Megan; Urbanek, Rebecca Ann; Xiao, Wenhua; McLaren,  
Frances Marie; Horchler, Carey Lynn

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047524	A1	20010705	WO 2000-SE2608	20001219 <--
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 2001024201	A5	20010709	AU 2001-24201	20001219 <--
EP 1244453	A1	20021002	EP 2000-987933	20001219 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			

10/518,503

JP 2003518500	T	20030610	JP 2001-548118	20001219 <--
EP 1577311	A1	20050921	EP 2005-5708	20001219 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
ZA 2002004779	A	20030915	ZA 2002-4779	20020613 <--
ZA 2002004781	A	20030915	ZA 2002-4781	20020613 <--
US 2003153571	A1	20030814	US 2002-168757	20021217 <--
PRIORITY APPLN. INFO.:			US 1999-171906P	P 19991223 <--
			US 2000-236785P	P 20000929 <--
			US 2000-236783P	P 20000929 <--
			EP 2000-987935	A3 20001219 <--
			WO 2000-SE2608	W 20001219 <--

OTHER SOURCE(S): MARPAT 135:92640

ED Entered STN: 06 Jul 2001

AB The title compds. [I; R1 = halo; A = CHR2(CH2)n (n = 0-2); R2 = alkyl; D = (un)substituted 5-6 membered heteroaryl or its benz-derivative having 1-3 ring atoms selected from N, O or S], useful for the treatment of pain, were prepared E.g., a multi-step synthesis of I.MeSO3H [R1 = 7-Cl; A = CHMe; D = 3-pyridyl] which showed Ki of 272 nM against binding to NMDA receptor glycine site, was given.

IC ICM A61K031-5025

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

ST pyridazinoquinolinedione prepn analgesic NMDA receptor glycine site

IT Glutamate receptors

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(NMDA-binding, glycine site; preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT Analgesics

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 349111-62-2P 349111-64-4P 349111-66-6P 349111-68-8P 349111-70-2P  
349111-72-4P 349111-73-5P 349111-75-7P 349111-77-9P 349111-79-1P  
349111-81-5P 349111-83-7P 349111-85-9P 349111-87-1P 349111-88-2P  
349111-89-3P 349111-90-6P 349111-91-7P 349111-92-8P  
349111-93-9P 349111-94-0P 349111-95-1P  
349111-96-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 75-26-3, 2-Bromopropane 88-15-3, 2-Acetylthiophene 100-48-1,  
4-Cyanopyridine 100-70-9, 2-Cyanopyridine 106-94-5, 1-Bromopropane  
123-75-1, Pyrrolidine, reactions 350-03-8, 3-Acetylpyridine 762-42-5,  
Dimethyl acetylenedicarboxylate 870-46-2, tert-Butyl carbazate  
872-85-5, 4-Pyridinecarboxaldehyde 926-62-5, Isobutylmagnesium bromide  
1122-54-9, 4-Acetylpyridine 1192-62-7, 2-Acetylfuran 1570-48-5,  
1-(3-Pyridyl)propan-1-one 1646-26-0, Benzofuran-2-yl methyl ketone  
1701-73-1, 1-(4-Pyridyl)pentan-1-one 5900-58-3, Methyl  
2-amino-4-chlorobenzoate 6602-54-6, 2-Chloro-3-cyanopyridine  
15871-85-9, 2-Methoxy-5-cyanopyridine 18781-31-2 22047-25-2,  
Acetylpyrazine 22720-75-8, 2-Acetylbenzothiophene  
22971-32-0, 1-(2-Pyridyl)butan-1-one 26414-90-4 27443-36-3  
33252-30-1, 2-Chloro-4-cyanopyridine 82736-91-2 88653-55-8,  
2-Acetyl-5-cyanothiophene 349112-16-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

IT 1701-71-9P 3238-55-9P 6952-53-0P 106728-59-0P 109352-68-3P  
 109352-88-7P 109352-93-4P 109352-96-7P 113143-16-1P 170143-39-2P  
 182887-52-1P 182887-56-5P 349110-82-3P 349111-97-3P 349111-98-4P  
 349112-00-1P 349112-01-2P 349112-02-3P 349112-03-4P 349112-04-5P  
 349112-05-6P 349112-06-7P 349112-07-8P 349112-08-9P 349112-09-0P  
 349112-10-3P 349112-11-4P 349112-12-5P 349112-13-6P 349112-14-7P  
 349112-15-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Zeneca Limited	1995			WO 9511244 A1	HCAPLUS
Zeneca Limited	1996			EP 0736531 A1	HCAPLUS

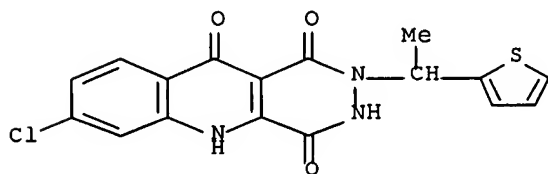
IT 349111-92-8P 349111-93-9P 349111-94-0P  
349111-95-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones for the treatment of pain)

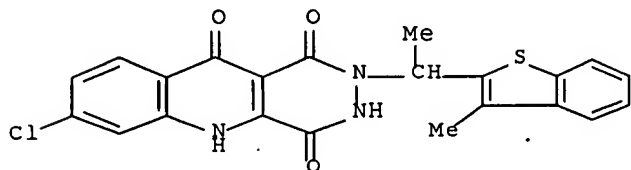
RN 349111-92-8 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 7-chloro-2,3-dihydro-2-[1-(2-thienyl)ethyl]- (9CI) (CA INDEX NAME)



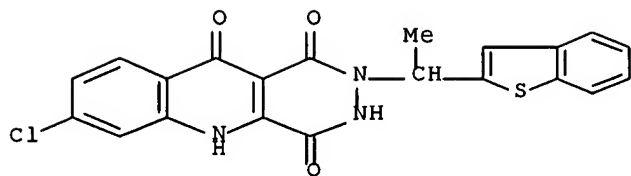
RN 349111-93-9 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 7-chloro-2,3-dihydro-2-[1-(3-methylbenzo[b]thien-2-yl)ethyl]- (9CI) (CA INDEX NAME)



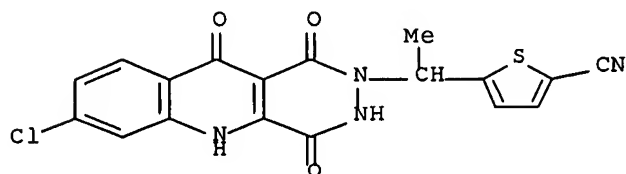
RN 349111-94-0 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 2-(1-benzo[b]thien-2-ylethyl)-7-chloro-2,3-dihydro- (9CI) (CA INDEX NAME)



RN 349111-95-1 HCAPLUS

CN 2-Thiophenecarbonitrile, 5-[1-(7-chloro-3,4,5,10-tetrahydro-1,4,10-trioxypyridazino[4,5-b]quinolin-2(1H)-yl)ethyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 16 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:416941 HCAPLUS Full-text

DOCUMENT NUMBER: 135:33489

TITLE: Pyrazolopyrazines and their use as adenosine antagonists

INVENTOR(S): Akahane, Atsushi; Kuroda, Satoru; Itani, Hiromichi; Tabuchi, Seiichiro; Sato, Yoshinori; Matsuoka, Nobuya; Tada, Miho; Matsuoka, Hideaki; Oku, Takuma; Tanaka, Akira

PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001040230	A1	20010607	WO 2000-JP8008	20001113 <--
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, VZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1244669	A1	20021002	EP 2000-974973	20001113 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,			

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
 JP 2003515537 T 20030507 JP 2001-540985 20001113 <--  
 PRIORITY APPLN. INFO.: AU 1999-4414 A 19991202 <--  
 WO 2000-JP8008 W 20001113 <--

OTHER SOURCE(S): MARPAT 135:33489

ED Entered STN: 08 Jun 2001

AB A pyrazolopyrazine compound of formula I is claimed [wherein R1 = (un)substituted aryl; R2 = H, lower alkyl, lower alkenyl, cyclo(lower)alkyl, heteromonocyclic group, lower alkyl (un)substituted by one or more of cyclo(lower)alkyl, halogen, cyano, aryl and heteromonocyclic group; or a salt thereof]. I are adenosine antagonists, and are useful for the prevention and/or treatment of a wide variety of conditions known to be related to adenosine receptors, including depression, dementia (e.g., Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure, and the like. Over 60 examples and various intermediates were prepared. For instance, 6-benzenesulfonyl-2H-pyridazin-3-one was converted to its O-triflate, which was coupled with phenylacetylene and then cyclized with 1-aminopyrazinium iodide to give 3-(6-benzenesulfonylpyridazin\*\* \* -3-yl)-2-phenylpyrazolo[1,5-a]pyrazine. The latter was hydrolyzed to

remove the benzenesulfonyl group and then coupled with 3-pyridinemethanol by Mitsunobu reaction to give title compound II. Six selected I bound to A1 and A2a receptors with Ki ranges of 0.06-0.16 nM and 0.84-3.17 nM, resp. Four compds. also gave complete or near-complete reversal of haloperidol-induced catalepsy in mice at 3.2 mg/kg.

IC ICM C07D487-04

ICS A61K031-495; A61P025-28; A61P025-16; A61P025-22; A61P009-04;  
 A61P001-04; A61P001-18; A61P013-12; A61P009-10

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1

ST pyrazolopyrazine prepn adenosine antagonist; anticataleptic  
 \*\*\*pyridazinyl pyrazolopyrazine prepn

IT	343792-04-1P	343792-05-2P	343792-06-3P	343792-07-4P	343792-08-5P
	343792-09-6P	343792-10-9P	343792-11-0P	343792-12-1P	343792-13-2P
	343792-14-3P	343792-15-4P	<b>343792-16-5P</b>	343792-17-6P	
	343792-18-7P	343792-19-8P	343792-20-1P	343792-21-2P	343792-22-3P
	343792-24-5P	343792-25-6P	343792-26-7P	343792-27-8P	343792-28-9P
	343792-29-0P	343792-30-3P	343792-32-5P	343792-33-6P	343792-34-7P
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	343792-65-4P	343792-66-5P	343792-67-6P	343792-68-7P	

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrazolopyrazines as adenosine antagonists)

# RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Akahane	1998			US 5773530 A	HCAPLUS
Fujisawa	1990			EP 0379979 A	HCAPLUS
Fujisawa	1992			EP 0467248 A	HCAPLUS

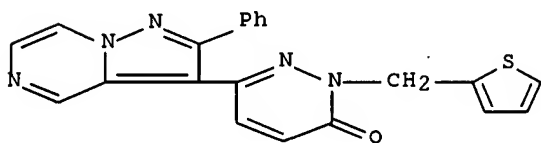
IT **343792-16-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrazolopyrazines as adenosine antagonists)

RN 343792-16-5 HCAPLUS

CN 3(2H)-Pyridazinone, 6-(2-phenylpyrazolo[1,5-a]pyrazin-3-yl)-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 17 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:772163 HCAPLUS Full-text

DOCUMENT NUMBER: 135:318510

TITLE: Preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors

INVENTOR(S): Black, Lawrence A.; Basha, Anwer; Kolasa, Teodozyj; Kort, Michael E.; Liu, Huaqing; McCarty, Catherine M.; Patel, Meena; Rohde, Jeffrey J.; Coghlan, Michael J.; Stewart, Andrew O.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: U.S., 129 pp., Cont.-in-part of U.S. Ser. No. 261,872, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6307047	B1	20011023	US 1999-427768	19991027 <--
TR 200000478	T2	20020422	TR 2000-200000478	19980810 <--
CA 2347982	A1	20000504	CA 1999-2347982	19991027 <--
WO 2000024719	A1	20000504	WO 1999-US25234	19991027 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9965230	A1	20000515	AU 1999-65230	19991027 <--
AU 773237	B2	20040520		
EP 1124804	A1	20010822	EP 1999-953259	19991027 <--
EP 1124804	B1	20050824		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9914858	A	20020205	BR 1999-14858	19991027 <--
TR 200101765	T2	20020221	TR 2001-200101765	19991027 <--
HU 200105248	A2	20020729	HU 2001-5248	19991027 <--
JP 2003512292	T	20030402	JP 2000-578289	19991027 <--
AT 302759	T	20050915	AT 1999-953259	19991027 <--

ES 2249919	T3	20060401	ES 1999-953259	19991027 <--
ZA 2001003310	A	20020723	ZA 2001-3310	20010423 <--
NO 2001002061	A	20010627	NO 2001-2061	20010426 <--
NO 318623	B1	20050418		
BG 105523	A	20011231	BG 2001-105523	20010519 <--
US 2002013318	A1	20020131	US 2001-871195	20010531 <--
US 2002028938	A1	20020307	US 2001-870838	20010531 <--
HK 1041876	A1	20060623	HK 2002-101207	20020219 <--
US 2003225276	A1	20031204	US 2003-417959	20030417 <--
US 7001895	B2	20060221		
US 2004158064	A1	20040812	US 2003-464928	20030619 <--
US 7115591	B2	20061003		
PRIORITY APPLN. INFO.:			US 1997-56733P	P 19970822 <--
			US 1998-129570	B2 19980805 <--
			US 1998-137457	B2 19980820 <--
			US 1998-179605	B2 19981027 <--
			US 1999-261872	B2 19990303 <--
			US 1997-917023	A 19970822 <--
			US 1999-298490	A 19990423 <--
			US 1999-427768	A 19991027 <--
			WO 1999-US25234	W 19991027 <--
			US 2001-870838	B3 20010531 <--
			US 2001-871195	B3 20010531 <--

OTHER SOURCE(S): MARPAT 135:318510

ED Entered STN: 24 Oct 2001

AB The title compds. [I; X = O, S, NR4, etc.; R4 = alkyl, alkenyl, cycloalkyl, etc.; R = H, alkyl, alkenyl, etc.; at least one of R1-R3 = II-III (wherein X1 = SO2, SO(NR10), SO, etc.; R9 = alkyl, alkenyl, alkynyl, etc.; X2 = H, halo, alkyl, etc.; R10 = H, alkyl, cycloalkyl); the remaining two of the groups of R1-R3 = H, OH, hydroxyalkyl, etc.] which are cyclooxygenase (COX) inhibitors, and in particular, are selective inhibitors of cyclooxygenase-2 (COX-2), and therefore are useful in treating pain, fever, inflammation, rheumatoid arthritis, and osteoarthritis, were prepared. Thus, oxidation of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (preparation given) with MeCO3H in CH2Cl2 afforded 86% I [X = O; R = PhCH2; R1 = 4-FC6H4; R2 = 4-(MeSO2)C6H4; R3 = H], which showed IC50 of 0.014  $\mu$ M against COX-2. COX-2 is the inducible isoform associated with inflammation, as opposed to the constitutive isoform, cyclooxygenase-1 (COX-1) which is an important "housekeeping" enzyme in many tissues, including the gastrointestinal (GI) tract and the kidneys. The selectivity of the compds. I for COX-2 minimizes the unwanted GI and renal side-effects seen with currently marketed non-steroidal anti-inflammatory drugs (NSAIDs).

IC ICM C07D237-16

ICS C07F009-6509; A61K031-50; A61K031-675

INCL 544240000

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST prostaglandin endoperoxide H synthase biosynthesis inhibitor  
arylpyridazinone prepn; arylpyridazinone prepn  
 prostaglandin endoperoxide H synthase biosynthesis inhibitor;  
 cyclooxygenase 2 selective inhibitor arylpyridazinone prepn;  
 analgesic arylpyridazinone prepn; antipyretic  
arylpyridazinone prepn; antiinflammatory arylpyridazinone  
 prepn; rheumatoid arthritis arylpyridazinone prepn;  
 osteoarthritis arylpyridazinone prepn; antiarthritic  
arylpyridazinone prepn

IT Analgesics

Anti-inflammatory agents

Antiarthritics

Antipyretics

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT Osteoarthritis

(treatment of; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 655-20-9P 2514-18-3P 14092-00-3P 28075-50-5P 34837-84-8P  
 40400-25-7P 51437-00-4P, 1-Bromo-4-fluoro-3-methylbenzene 59982-04-6P  
 63031-77-6P 84956-71-8P 89981-03-3P 97137-16-1P 98546-51-1P  
 109715-47-1P 134965-39-2P 161886-22-2P, 3,4-Difluorophenylhydrazine  
 213764-19-3P 221025-49-6P 221025-50-9P 221025-51-0P 221030-72-4P  
 221030-73-5P 221030-74-6P 221030-75-7P 221030-76-8P 221030-77-9P  
 221030-78-0P 221030-79-1P 221030-80-4P 221030-81-5P 221030-82-6P  
 221030-83-7P 221030-84-8P 221030-85-9P 221030-86-0P 221030-87-1P  
 221030-88-2P 221030-89-3P 221030-90-6P 221030-91-7P 221030-92-8P  
 221030-93-9P 221030-94-0P 221030-95-1P 221030-96-2P 221030-97-3P  
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 221031-03-4P 221031-04-5P 221031-05-6P 221031-06-7P 221031-07-8P  
 221031-08-9P 221031-09-0P 221031-10-3P 221031-11-4P 221031-12-5P  
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 221031-33-0P 221031-34-1P 221031-35-2P 221031-36-3P 221031-37-4P  
 221031-38-5P 221031-39-6P 221031-40-9P 221031-41-0P 266320-87-0P  
 266320-88-1P 266320-89-2P 266320-90-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 39391-18-9, Prostaglandin endoperoxide H synthase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 109715-46-0 266320-84-7 266320-85-8 266320-86-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 221031-64-7P 221031-65-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

IT 62-53-3, Benzenamine, reactions 65-85-0, Benzoic acid, reactions  
 67-63-0, 2-Propanol, reactions 70-11-1, 2-Bromoacetophenone 71-36-3,  
 n-Butanol, reactions 75-31-0, 2-Aminopropane, reactions 75-33-2,  
 Isopropyl mercaptan 75-65-0, Tert-Butanol, reactions 75-66-1,  
 2-Methyl-2-propanethiol 75-84-3 78-83-1, Reactions, reactions  
 87-56-9, Mucochloric acid 92-66-0, 4-Bromobiphenyl 92-69-3,  
 4-Phenylphenol 96-41-3, Cyclopentanol 97-95-0, 2-Ethyl-1-butanol  
 98-00-0, 2-(Hydroxymethyl)furan 98-02-2, Furfuryl mercaptan 98-59-9,  
 p-Toluenesulfonyl chloride 99-07-0, 3-(Dimethylamino)phenol 100-11-8  
 100-39-0 100-44-7, reactions 100-51-6, Benzyl alcohol, reactions  
 100-53-8, Benzyl mercaptan 101-55-3, 4-Bromodiphenylether 102-56-7,  
 2,5-Dimethoxyaniline 103-63-9, (2-Bromoethyl)benzene 103-67-3,  
 N-Methylbenzylamine 103-90-2 104-76-7 104-95-0, 4-Bromothioanisole  
 106-37-6, 1,4-Dibromobenzene 106-38-7, 1-Bromo-4-methylbenzene  
 106-39-8, 4-Bromo-1-chlorobenzene 106-41-2, p-Bromophenol 106-48-9,  
 p-Chlorophenol 106-96-7, Propargyl bromide 107-18-6, 2-Propen-1-ol,  
 reactions 107-82-4, 1-Bromo-3-methylbutane 108-01-0 108-11-2,  
 4-Methyl-2-pentanol 108-36-1, 1,3-Dibromobenzene 108-37-2,

1-Bromo-3-chlorobenzene 108-85-0, Cyclohexyl bromide 108-91-8,  
 Cyclohexanamine, reactions 108-93-0, Cyclohexanol, reactions 108-94-1,  
 Cyclohexanone, reactions 108-95-2, Phenol, reactions 109-00-2,  
 3-Hydroxypyridine 109-59-1, 2-(Isopropoxy)ethanol 110-63-4,  
 1,4-Butanediol, reactions 110-87-2 110-89-4, Piperidine, reactions  
 110-91-8, Morpholine, reactions 116-09-6, Acetol 120-20-7,  
 3,4-Dimethoxyphenethylamine 123-51-3 123-75-1, Pyrrolidine, reactions  
 126-30-7 137-43-9, Cyclopentyl bromide 150-76-5, 4-Methoxyphenol  
 151-18-8 156-87-6, 3-Hydroxypropylamine 339-62-8 348-57-2,  
 2,4-Difluorobromobenzene 348-61-8, 1-Bromo-3,4-difluorobenzene  
 349-55-3, 3-Methoxy-5-(trifluoromethyl)aniline 352-13-6,  
 4-Fluorophenylmagnesium bromide 352-34-1, 4-Fluoriodobenzene  
 353-83-3, 2-Iodo-1,1,1-trifluoroethane 363-80-4, 2,3,5-Trifluoroaniline  
 367-11-3, 1,2-Difluorobenzene 367-25-9, 2,4-Difluoroaniline 367-67-9,  
 2-Bromo-5-nitrobenzotrifluoride 368-78-5, 3-  
 (Trifluoromethyl)phenylhydrazine 371-14-2 371-40-4, 4-Fluoroaniline  
 371-41-5, 4-Fluorophenol 372-19-0, 3-Fluoroaniline 372-20-3,  
 3-Fluorophenol 383-53-9, 2-Bromo-4'-(trifluoromethyl)acetophenone  
 395-44-8, 2-(Trifluoromethyl)benzyl bromide 401-81-0 402-43-7,  
 1-Bromo-4-trifluoromethylbenzene 403-41-8, 4-Fluoro- $\alpha$ -methylbenzyl  
 alcohol 405-50-5, 4-Fluorophenylacetic acid 456-41-7, 3-Fluorobenzyl  
 bromide 459-46-1, 4-Fluorobenzyl bromide 460-25-3,  
 1,3-Dibromo-1,1-difluoropropane 461-96-1, 3,5-Difluorobromobenzene  
 488-11-9, Mucobromic acid 513-44-0, 2-Methyl-1-propanethiol 536-38-9,  
 2-Bromo-4'-chloroacetophenone 541-73-1 556-96-7, 5-Bromo-m-xylene  
 558-43-0, 2-Methyl-1,2-propanediol 563-47-3, 3-Chloro-2-methylpropene  
 577-19-5, 1-Bromo-2-nitrobenzene 589-35-5 590-90-9,  
 4-Hydroxy-2-butanone 591-17-3, 3-Bromotoluene 600-36-2,  
 2,4-Dimethyl-3-pentanol 619-57-8, 4-Hydroxybenzamide 622-26-4,  
 4-(2-Hydroxyethyl)piperidine 622-40-2, 4-(2-Hydroxyethyl)morpholine  
 623-00-7, 4-Bromobenzonitrile 624-95-3, 3,3-Dimethyl-1-butanol  
 626-88-0, 1-Bromo-4-methylpentane 626-89-1, 4-Methyl-1-pentanol  
 627-59-8, 5-Methyl-2-hexanol 636-98-6, 1-Iodo-4-nitrobenzene 645-56-7,  
 4-(n-Propyl)phenol 661-69-8, Hexamethylditin 700-57-2, 2-Adamantanol  
 701-34-8, 4-Aminosulfonyl-1-bromobenzene 763-32-6 763-89-3 765-58-2,  
 2-Bromo-5-methylthiophene 766-00-7, Cyclopentaneethanol  
 766-02-9, 2-Cyclopentene-1-ethanol 767-00-0, 4-Cyanophenol 823-85-8,  
 4-Fluorophenylhydrazine hydrochloride 870-63-3 873-74-5,  
 4-Aminobenzonitrile 924-41-4, 1,5-Hexadien-3-ol 931-51-1,  
 Cyclohexylmagnesium chloride 1003-03-8, Cyclopentylamine 1003-09-4, 2-  
Bromothiophene 1072-85-1, 2-Fluorobromobenzene 1073-62-7,  
 Benzylhydrazine hydrochloride 1121-86-4, 1-Fluoro-3-iodobenzene  
 1126-81-4, 4-Acetamidothiophenol 1423-26-3 1462-03-9,  
 1-Methyl-1-cyclopentanol 1521-51-3, 3-Bromocyclohexene 1544-53-2  
 1569-69-3, Cyclohexyl mercaptan 1643-73-8, 4-Fluorobenzylmagnesium  
 chloride 1679-07-8, Cyclopentyl mercaptan 1679-18-1,  
 4-Chlorobenzeneboronic acid 1698-53-9, 2-Phenyl-4,5-dichloro-3(2H)-  
pyridazinone 1765-40-8, 2,3,4,5,6-Pentafluorobenzyl bromide  
 1765-93-1, 4-Fluorobenzeneboronic acid 1794-48-5 1826-67-1,  
 Vinylmagnesium bromide 1996-29-8, 1-Bromo-4-chloro-2-fluorobenzene  
 2039-86-3, 3-Bromostyrene 2076-88-2, 2-(Chloromethyl)benzo[b]  
thiophene 2081-44-9, 4-Tetrahydropyranol 2113-57-7,  
 3-Bromobiphenyl 2156-04-9 2259-30-5, Tert-Butylmagnesium bromide  
 2312-23-4, 3-Chlorophenylhydrazine hydrochloride 2357-52-0,  
 3-Fluoro-4-methoxybromobenzene 2417-72-3, Methyl 4-(bromomethyl)benzoate  
 2516-33-8, Cyclopropylmethanol 2516-34-9, Cyclobutanamine 2516-47-4,  
 Cyclopropanemethanamine 2517-43-3 2557-78-0, 2-  
Fluorothiophenol 2566-44-1, 2-(Cyclopropyl)ethanol 2567-14-8,  
 1,1,3-Trichloropropene 2568-33-4 2637-34-5, 2-Mercaptopyridine  
 2746-14-7, 1-Methylcyclopropanemethanol 2746-23-8, 3-(Chloromethyl)

thiophene 2799-16-8 2873-18-9, 2-Bromo-5-  
chlorothiophene 2924-16-5, 3-Fluorophenylhydrazine hydrochloride  
 2938-98-9, 2-Methyl-1,4-butanediol 3179-31-5, 1H-1,2,4-Triazole-3-thiol  
 3446-89-7, 4-Methylthiobenzaldehyde 3863-11-4 3958-57-4, 3-Nitrobenzyl  
 bromide 3972-65-4, 1-Bromo-4-tert-butylbenzene 4254-29-9, 2-Indanol  
 4294-57-9, p-Tolylmagnesium bromide 4377-41-7, 2-(Chloromethyl)quinoline  
 4392-24-9, Cinnamyl bromide 4399-47-7, Cyclobutyl bromide 4548-78-1,  
 3-Methylbutylmagnesium bromide 4795-29-3, Tetrahydrofurfurylamine  
 5036-48-6, 1H-Imidazole-1-propanamine 5042-30-8, Trifluoroethylhydrazine  
 5271-38-5, 2-(Methylthio)ethanol 5332-73-0, 3-Methoxypropylamine  
 5362-55-0 5469-26-1, 1-Bromopinacolone 5673-98-3 5674-02-2,  
 Isobutylmagnesium chloride 5713-61-1, 2-Thienylmagnesium bromide  
 5720-05-8, 4-Methylphenylboronic acid 5720-06-9, 2-Methoxybenzenboronic  
 acid 5788-58-9, 4,5-Dibromo-3(2H)-pyridazinone 6165-69-1,  
Thiophene-3-boronic acid 6351-10-6, 1-Indanol 6630-33-7,  
 2-Bromobenzaldehyde 6738-06-3, Phenylacetylenemagnesium bromide  
 6921-34-2, Benzylmagnesium chloride 7051-34-5 7342-82-7, 3-  
Bromobenzothiophene 7400-27-3, Tert-Butylhydrazine hydrochloride  
 7417-21-2, 2-(3,4-Dimethoxyphenyl)ethanol 7429-94-9 10493-44-4  
 13124-18-0, 3,4-Dichlorophenylhydrazine 13195-50-1, 2-Bromo-5-  
nitrothiophene 13291-18-4, Isopropenylmagnesium bromide  
 13331-27-6, 3-Nitrobenzenboronic acid 14114-05-7,  
 Cyclopropyltriphenylphosphonium bromide 14282-76-9, 2-Bromo-3-  
methylthiophene 14300-71-1 14763-20-3 14763-60-1,  
 4-(Methylsulfonyl)phenol 14916-80-4, 3-Octyn-1-ol 15894-04-9  
 16419-60-6 16466-97-0 18729-48-1, 3-Methylcyclopentanol 19477-73-7,  
 6-Bromophthalide 19614-16-5, 2-Bromothioanisole 20099-89-2,  
 2-Bromo-4'-cyanoacetophenone 22037-28-1, 3-Bromofuran 22884-29-3,  
 Isobutyltriphenylphosphonium bromide 23915-07-3, 2,4-Difluorobenzyl  
 bromide 24070-77-7, 2-Methylcyclopentanol 26167-44-2,  
 3-Chloroacetylbenzo[b]thiophene 26445-03-4, Thiocresol  
 27246-81-7, 3-Bromophenylhydrazine hydrochloride 27314-17-6  
 28322-40-9, Isoamyltriphenylphosphonium bromide 32916-51-1,  
 Cyclopentylmagnesium chloride 33577-16-1, Methyl(methylsulfinylmethyl)su  
 lfide 33598-19-5 33733-73-2, 3-Bromothioanisole 33884-43-4,  
 2-(2-Bromoethyl)-1,3-dioxane 34698-41-4, 1-Indanylamine  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (reactant; preparation of arylpyridazinones as prostaglandin  
 endoperoxide H synthase biosynthesis inhibitors)  
 IT 35166-78-0, Cyclohexylmethylmagnesium bromide 37677-17-1,  
 1-Bromomethylcyclohexene 39720-27-9, 4-(Chloromethyl)phenyl acetate  
 40594-37-4, 3,4-Difluorophenylhydrazine hydrochloride 40811-49-2,  
 2-(Isopropylthio)ethanol 50398-79-3, 2-(Bromomethyl)-5-  
chlorothiazole 51336-94-8, 2-Chloro-2',4'-difluoroacetophenone  
 51755-66-9, 3-(Methylthio)-1-hexanol 52497-07-1, 1,3-Dichloro-1-butene  
 54751-01-8, 4-(Bromomethyl)pyridine 55401-97-3, 2-(Bromomethyl)pyridine  
 55499-43-9 55766-17-1 56816-01-4, Ethyl (S)-3-hydroxybutanoate  
 58114-09-3 59311-22-7 59311-24-9 60811-18-9, 4-Bromo-1-chloro-2-  
 fluorobenzene 60811-21-4 60811-23-6, 3-Chloro-4-  
fluorothiophenol 62087-82-5, 1-Adamantyl fluoroformate  
 64168-34-9, 3-Fluorobenzylmagnesium chloride 65130-46-3 69966-55-8,  
 3-(Bromomethyl)pyridine 72396-61-3 72657-23-9 80657-57-4, Methyl  
 (S)-3-hydroxy-2-methylpropionate 82297-89-0, 4-Fluoro-3-  
 methylphenylmagnesium bromide 84282-78-0 85118-01-0,  
 3,4-Difluorobenzyl bromide 85676-85-3 90555-66-1 90878-19-6,  
 Phenethylmagnesium chloride 92636-36-7 93777-26-5,  
 5-Bromo-2-fluorobenzaldehyde 98437-24-2, 2-Benzofuranboronic acid  
 103962-10-3, 2-Bromo-4'-(trifluoromethoxy)acetophenone 112615-82-4,  
 5-Methylhexylmagnesium bromide 122957-82-8 124050-15-3,  
 2-(Chloromethyl)-6-fluoroquinoline 128758-41-8 128796-39-4,

4-(Trifluoromethyl)benzenboronic acid 134150-01-9 137504-86-0,  
 3-Fluoro-4-chlorophenylboronic acid 141483-15-0, 2-Fluoro-5-  
 trifluoromethylphenol 144432-85-9, 3-Chloro-4-fluorobenzenboronic acid  
 149507-26-6 151411-98-2 157911-55-2 157911-56-3 162125-08-8,  
 3,4-Dichlorophenylboronic acid 162607-18-3 163105-90-6 168267-99-0  
 171497-20-4 172975-69-8 175135-73-6 175135-74-7 208641-98-9  
 221020-96-8 221031-42-1 221031-43-2 221031-44-3 221031-45-4  
 221031-46-5 221031-47-6 221031-48-7 221031-49-8 221031-50-1  
 221031-51-2 221031-52-3 221031-53-4 221031-54-5 221031-55-6  
 221031-56-7 221031-57-8 221031-58-9 221031-59-0 221031-60-3  
 221031-61-4 221031-62-5 221031-63-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of arylpyridazinones as prostaglandin  
 endoperoxide H synthase biosynthesis inhibitors)

IT	213763-90-7P	213764-00-2P	213764-17-1P	221025-44-1P	221025-45-2P
	221025-46-3P	221025-47-4P	221025-52-1P	221025-53-2P	221025-77-0P
	221026-16-0P	221026-30-8P	221026-34-2P	221026-35-3P	221026-45-5P
	221026-46-6P	221026-51-3P	221026-61-5P	221026-62-6P	221026-78-4P
	221027-19-6P	221027-24-3P	221027-36-7P	221027-91-4P	221027-98-1P
	221028-16-6P	221028-18-8P	221028-23-5P	221028-31-5P	221028-43-9P
	221028-45-1P	221029-22-7P	221029-24-9P	221029-25-0P	221029-26-1P
	221029-28-3P	221029-32-9P	221029-41-0P	221029-43-2P	221029-46-5P
	221029-47-6P	221029-50-1P	221029-69-2P	221029-78-3P	221029-80-7P
	221029-81-8P	221029-83-0P	221029-84-1P	221029-86-3P	221030-47-3P
	221030-56-4P	221030-64-4P	221030-66-6P	221030-67-7P	266320-83-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT  
 (Reactant or reagent); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin  
 endoperoxide H synthase biosynthesis inhibitors)

IT	213763-92-9P	213763-94-1P	213763-98-5P	213763-99-6P	213764-11-5P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

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 266320-17-6P 266320-18-7P 266320-19-8P 266320-20-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
=====	=====	=====	=====	=====	=====
Anon	1988			WO 8809675	HCAPLUS
Anon	1996			EP 0711759	HCAPLUS
Anon	1996			EP 0714895	HCAPLUS
Anon	1999			WO 9910331	HCAPLUS
Griswold	1986	16	181	Medicinal Research R	
Li	1999			US 6004960	HCAPLUS
Sircar	1983			US 4404203	HCAPLUS
Vane	1994	367	215	Nature	MEDLINE

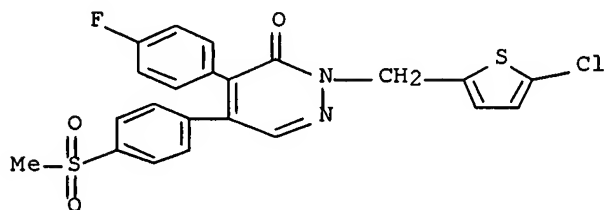
IT 221025-73-6P 221025-74-7P 221025-98-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of arylpyridazinones as prostaglandin endoperoxide H synthase biosynthesis inhibitors)

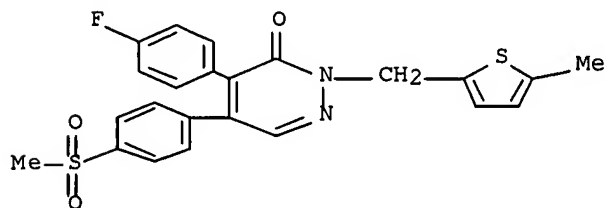
RN 221025-73-6 HCAPLUS

CN 3(2H)-Pyridazinone, 2-[(5-chloro-2-thienyl)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



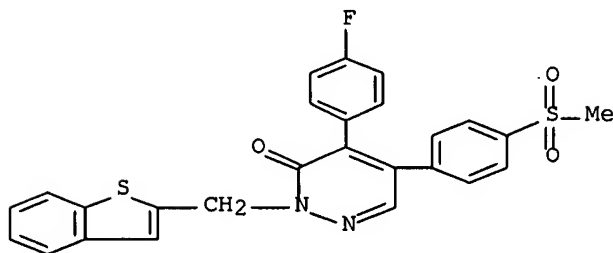
RN 221025-74-7 HCAPLUS

CN 3(2H)-Pyridazinone, 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



RN 221025-98-5 HCAPLUS

CN 3 (2H)-Pyridazinone, 2-(benzo[b]thien-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 18 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:635750 HCAPLUS Full-text

DOCUMENT NUMBER: 129:275920

TITLE: Preparation of pyridazinones as inhibitors of cyclooxygenase-2

INVENTOR(S): Li, Chun Sing; Prasit, Petpiboon; Gauthier, Jacques Y.; Lau, Cheuk K.; Therien, Michel

PATENT ASSIGNEE(S): Merck Frosst Canada Inc., Can.

SOURCE: PCT Int. Appl., 87 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841511	A1	19980924	WO 1998-CA233	19980312 <--
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2283399	A1	19980924	CA 1998-2283399	19980312 <--
CA 2283399	C	20060221		
AU 9864913	A	19981012	AU 1998-64913	19980312 <--
AU 738727	B2	20010927		
EP 975604	A1	20000202	EP 1998-910544	19980312 <--
EP 975604	B1	20040721		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001514669	T	20010911	JP 1998-539982	19980312 <--
AT 271547	T	20040815	AT 1998-910544	19980312 <--
ES 2224366	T3	20050301	ES 1998-910544	19980312 <--
US 6004960	A	19991221	US 1998-42174	19980313 <--
PRIORITY APPLN. INFO.:			US 1997-40791P	P 19970314 <--
			GB 1997-7487	A 19970414 <--
			WO 1998-CA233	W 19980312 <--

OTHER SOURCE(S): MARPAT 129:275920

ED Entered STN: 08 Oct 1998

- AB The title compds. [I; X = a bond, (CH<sub>2</sub>)<sub>m</sub> (m = 1-2); CO, etc.; R<sub>1</sub> = Me, NH<sub>2</sub>. NHC(O)CF<sub>3</sub>; R<sub>2</sub> = (CR<sub>6</sub>R<sub>7</sub>)<sub>n</sub>R<sub>8</sub> (R<sub>6</sub>, R<sub>7</sub> = H, C<sub>1</sub>-10 alkyl, C<sub>1</sub>-10 fluoroalkyl; R<sub>8</sub> = C<sub>1</sub>-10 alkyl, (un)substituted Ph, naphthyl, etc.); R<sub>3</sub> = C<sub>1</sub>-10 alkyl, (un)substituted Ph, naphthyl, etc.; R<sub>4</sub> = H, halo, C<sub>1</sub>-6 alkyl], useful in treating an inflammatory disease susceptible to treatment with a non-steroidal antiinflammatory agent, and cyclooxygenase-2 mediated diseases, were prepared. Thus, reaction of 5-hydroxy-4-(4-methylsulfonyl)phenyl-3-phenyl-5H-furan-2-one with phenylhydrazine in EtOH afforded 30% I [X = a bond; R<sub>1</sub> = Me; R<sub>2</sub> = Ph; R<sub>3</sub> = Ph; R<sub>4</sub> = H] which showed IC<sub>50</sub> of 0.08 against COX-2 using CHO cell line assay.
- IC ICM C07D237-04  
ICS A61K031-50
- CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1
- ST pyridazinone prepn cyclooxygenase selective inhibitor;  
antiinflammatory pyridazinone prepn
- IT Anti-inflammatory agents  
(treating an inflammatory disease susceptible to treatment with a non-steroidal antiinflammatory agent; preparation of pyridazinones as inhibitors of cyclooxygenase-2)
- IT 39391-18-9  
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
(2; selective COX-2 inhibitor; preparation of pyridazinones as inhibitors of cyclooxygenase-2)
- IT 213763-79-2P 213763-80-5P 213763-81-6P 213763-82-7P 213763-83-8P  
213763-84-9P 213763-85-0P 213763-86-1P 213763-87-2P 213763-88-3P  
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213764-08-0P 213764-09-1P 213764-10-4P 213764-11-5P 213764-12-6P  
213764-13-7P 213764-14-8P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of pyridazinones as inhibitors of cyclooxygenase-2)
- IT 67-63-0, Isopropanol, reactions 75-30-9, 2-Iodopropane 96-32-2, Methyl bromoacetate 100-39-0, Benzyl bromide 100-63-0, Phenylhydrazine 345-35-7, 2-Fluorobenzyl chloride 371-41-5, 4-Fluorophenol 456-42-8, 3-Fluorobenzyl chloride 459-46-1, 4-Fluorobenzyl bromide 460-37-7, 3,3,3-Trifluoropropyl iodide 461-17-6, 4,4,4-Trifluorobutyl iodide 488-11-9, Mucobromic acid 513-38-2, 2-Methylpropyl iodide 585-71-7, (1-Bromoethyl)benzene 626-55-1, 3-Bromopyridine 630-17-1, 2,2-Dimethylpropyl bromide 1822-51-1, 4-Chloromethylpyridine hydrochloride 2417-72-3, 4-Carbomethoxybenzyl bromide 2550-36-9, Bromomethylcyclohexane 2924-16-5, 3-Fluorophenylhydrazine hydrochloride 3510-66-5, 2-Bromo-5-methylpyridine 4214-79-3, 5-Chloro-2-pyridinol 5042-30-8, 2,2,2-Trifluoroethylhydrazine 5419-55-6 5788-58-9 6959-47-3, 2-Picolyl chloride hydrochloride 7051-34-5, (Bromomethyl)cyclopropane 17247-58-4, Bromomethylcyclobutane 20570-96-1, Benzylhydrazine dihydrochloride 45438-73-1, 2-(Bromomethyl)thiophene 98546-51-1, 4-(Methylthio)phenylboronic acid 185147-17-5 185147-18-6 189956-44-3 213764-23-9 213764-24-0 213764-25-1  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of pyridazinones as inhibitors of cyclooxygenase-2)
- IT 134965-39-2P 213764-15-9P 213764-16-0P 213764-17-1P 213764-18-2P  
213764-19-3P 213764-20-6P 213764-21-7P 213764-22-8P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(preparation of pyridazinones as inhibitors of cyclooxygenase-2)

## RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Diamond Shamrock Corp	1983			WO 8300863 A	HCAPLUS
Merck Frosst Canada Inc	1995			WO 9518799 A	HCAPLUS
Merck Frosst Canada Inc	1996			WO 9606840 A	HCAPLUS
Nissan Chemical Ind Ltd	1990			EP 0376079 A	HCAPLUS
Partis, R	1996			WO 9624584 A	HCAPLUS
Searle & Co	1996			WO 9641626 A	HCAPLUS
Searle & Co	1996			WO 9641645 A	HCAPLUS
Yves, G	1995			WO 9500501 A	HCAPLUS
Yves, G	1998			WO 9803484 A	HCAPLUS

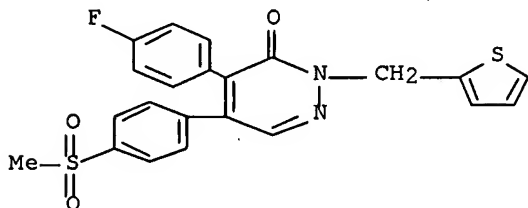
IT 213764-05-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyridazinones as inhibitors of cyclooxygenase-2)

RN 213764-05-7 HCAPLUS

CN 3(2H)-Pyridazinone, 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 19 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:186492 HCAPLUS Full-text

DOCUMENT NUMBER: 128:230388

TITLE: Preparation of 4-aminopyrimidines for control of diabetic complications.

INVENTOR(S): Mylari, Banavara L.; Oates, Peter J.; Siegel, Todd W.; Zembrowski, William J.

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: U.S., 30 pp., Cont.-in-part of U.S. Ser. No. 952,222, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5728704	A	19980317	US 1995-406947	19950324 <--
WO 9407867	A1	19940414	WO 1993-US6446	19930712 <--
W: AU, CA, JP, KR, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

10/518,503

IL 121837	A	20030312	IL 1993-121837	19930923 <--
US 5866578	A	19990202	US 1997-980559	19971201 <--
PRIORITY APPLN. INFO.:			US 1992-952222	B2 19920928 <--
			WO 1993-US6446	W 19930712 <--
			IL 1993-107085	A3 19930923 <--
			US 1995-406947	A1 19950324 <--

OTHER SOURCE(S): MARPAT 128:230388

ED Entered STN: 30 Mar 1998

AB Title compds. [I; R1 = H, CF3, alkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl, alkoxy, Ph, naphthyl, etc.; R2, R3 = H, alkyl, (substituted) Ph, phenylalkyl; R2R3N = (substituted) azetidino, pyrrolidino, piperidino, piperazino, morpholino; R4 = H, Cl, Br, cyano, NO2, CF3, amino, alkyl, hydroxyalkyl, alkoxy, (substituted) Ph, naphthyl, furyl; R5 = H, alkyl, alkoxy, CF3, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, (substituted) Ph, furyl], were prepared Thus, 4-[4-(N-methylsulfamoyl)piperazino]-2-hydroxymethylpyrimidine (bioprepn. given) inhibited sorbitol dehydrogenase with IC50 = 1  $\mu$ M.

IC ICM A71K031-505

ICS C07D401-04

INCL 514256000

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT 204456-53-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 4-aminopyrimidines for control of diabetic complications)

IT 131816-54-1 140687-51-0 204456-54-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 4-aminopyrimidines for control of diabetic complications)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Albeck	1992			US 5102908	HCAPLUS
Anon	1954			FR 1063014	
Anon	1964			GB 0959699	
Anon	1982			EP 0047190	
Anon	1982			EP 0055693	HCAPLUS
Anon	1987			EP 0218999	HCAPLUS
Anon	1990			EP 0384370	HCAPLUS
Anon	1992			EP 0470616	HCAPLUS
Anon	1992			EP 9204333	
Brittain	1981			US 4251528	HCAPLUS
Brittain	1992			US 5110808	HCAPLUS
Brown	1992			US 5102905	HCAPLUS
Eggler	1991			US 5039672	HCAPLUS
Geisen	1992			US 5138058	HCAPLUS
Larson	1990			US 4939140	HCAPLUS
Lipinski	1989			US 4835410	
Lipinski	1991			US 5066659	HCAPLUS
Mallion	1992			US 5096918	HCAPLUS
Mattson	1992			US 5098904	HCAPLUS
Mylari	1991			US 4996204	HCAPLUS
Mylari	1991	34	109	Journal of Medicinal	
Mylari	1992	35	2155	Journal of Medicinal	HCAPLUS
Mylari	1992	35	457	Journal of Medicinal	HCAPLUS
Sarges	1978			US 4130714	HCAPLUS
Sestanj	1984			US 4439617	HCAPLUS
Yanagisawa	1988			US 4734410	HCAPLUS

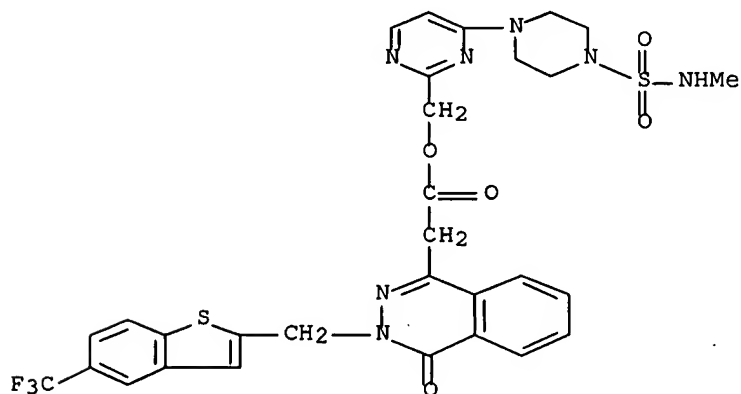
York | 1989 | | US 4864028 | HCAPLUS

IT **204456-53-1P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 4-aminopyrimidines for control of diabetic complications)

RN 204456-53-1 HCAPLUS

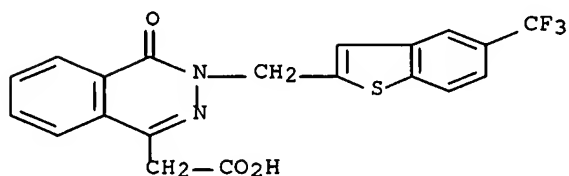
CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)benzo[b]thien-2-yl)methyl]-, [4-[4-[(methylamino)sulfonyl]-1-piperazinyl]-2-pyrimidinyl)methyl ester (9CI)  
(CA INDEX NAME)

IT **204456-54-2**

RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of 4-aminopyrimidines for control of diabetic complications)

RN 204456-54-2 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)benzo[b]thien-2-yl)methyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 20 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:719673 HCAPLUS Full-text

DOCUMENT NUMBER: 128:13276

TITLE: 1-(Arylsulfonyl)-, 1-(arylcarbonyl)-, and  
1-(arylphosphonyl)-3-phenyl-1,4,5,6-  
tetrahydropyridazines

INVENTOR(S): Combs, Donald W.

PATENT ASSIGNEE(S): Ortho Pharmaceutical Corp., USA

SOURCE: U.S., 28 pp., Cont.-in-part of U.S. Ser. No. 80,986,  
abandoned.

CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5684151	A	19971104	US 1995-362476	19950306 <--
WO 9401412	A1	19940120	WO 1993-US6394	19930701 <--

W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SE, SK, UA  
 RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, BG, CI, CM, GA, GN

PRIORITY APPLN. INFO.:  
 US 1992-906984 B1 19920701 <--  
 US 1993-80986 B2 19930621 <--  
 WO 1993-US6394 W 19930701 <--

ED Entered STN: 14 Nov 1997

AB Title compds. such as I [R = 2-naphthyl, (un)substituted Ph, 2-thienyl; R1 = H, Me; W = a bond, CH:CH; R2 = (un)substituted Ph, 2-naphthyl] were prepared. Progestin receptor binding, progestational and antiprogestational activity, osteoblast cell proliferation, and CNS receptor binding of the products were determined.

IC ICM C07D237-04  
 ICS C07D409-04; C07D237-26

INCL 544224000

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1

ST pyridazine arylsulfonyl arylcarbonyl arylphosphonyl prepn bioactivity; progestin agonist tetrahydropyridazine derivs; bone growth activity tetrahydropyridazine derivs; CNS receptor binding tetrahydropyridazine derivs; receptor progestin CNS binding tetrahydropyridazine derivs

IT Progesterone receptors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazine binding to)

IT Receptors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (CNS; 1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazine binding to)

IT Nervous system  
 (central, receptors; 1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazine binding to CNS receptors)

IT Osteoblast  
 (growth; 1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazine effects on)

IT 159798-97-7P 159798-98-8P 159799-02-7P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)

IT 71094-17-2P 109809-47-4P 159797-68-9P 159797-69-0P 159797-70-3P  
 159797-71-4P 159797-72-5P 159797-73-6P 159797-74-7P 159797-75-8P  
 159797-76-9P 159797-77-0P 159797-78-1P 159797-79-2P 159797-80-5P  
 159797-81-6P 159797-82-7P 159797-83-8P 159797-84-9P 159797-85-0P

159797-86-1P	159797-87-2P	159797-88-3P	159797-89-4P	159797-90-7P
159797-91-8P	159797-92-9P	159797-93-0P	159797-94-1P	159797-95-2P
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159800-03-0P	159800-04-1P	159800-05-2P	159800-06-3P	159800-07-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

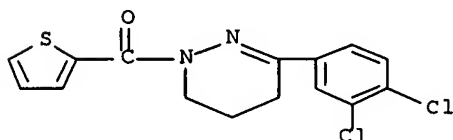
(1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)

IT 159800-08-5P	159800-09-6P	159800-10-9P	159800-11-0P	159800-12-1P
159800-13-2P	159800-14-3P	159800-15-4P	159800-16-5P	159800-17-6P
159800-18-7P	159800-19-8P	159800-20-1P	<u>159800-21-2P</u>	
159800-22-3P	159800-23-4P	159800-24-5P	159800-25-6P	159800-26-7P
159800-27-8P	159800-28-9P	159800-29-0P	159800-30-3P	159800-31-4P
159800-32-5P	159800-33-6P	159800-34-7P	159800-35-8P	199166-16-0P
199166-17-1P	199166-18-2P	199166-19-3P		

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)

- IT 77-73-6 95-13-6, Indene 98-60-2, Benzenesulfonyl chloride, 4-chloro-98-61-3, Benzenesulfonyl chloride, 4-iodo- 378-77-8, Propanoic acid, pentafluoro-, sodium salt 527-69-5, 2-Furoyl chloride 532-27-4, 2-Chloroacetophenone 536-38-9, 2-Bromo-4'-chloroacetophenone 542-92-7, 1,3-Cyclopentadiene, reactions 672-75-3, Benzoyl chloride, 3-bromo-4-fluoro- 824-72-6, Phenylphosphonic dichloride 832-53-1, Benzenesulfonyl chloride, pentafluoro- 931-57-7, 1-Methoxycyclohexene 1314-80-3, Phosphorus pentasulfide 1576-35-8, p-Toluenesulfonyl hydrazide 2751-27-1, Benzenesulfonic acid, 4-iodo-, hydrazide 3024-72-4, Benzoyl chloride, 3,4-dichloro- 3140-93-0, Thiophene, 2,3-dibromo- 3984-34-7 4083-64-1, Tosyl isocyanate 5271-67-0, 2-Thiophenecarbonyl chloride 6335-44-0 15988-11-1, 4-Phenylurazole 18523-22-3, 2,3'-Dibromoacetophenone 52240-00-3 159800-62-1 159800-73-4 199166-21-7 199166-22-8
- RL: RCT (Reactant); RACT (Reactant or reagent)  
(1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)
- IT 1011-46-7P 1017-06-7P 1079-73-8P 24734-44-9P 36725-34-5P 36725-37-8P 52239-89-1P 52239-91-5P 52239-99-3P 66548-93-4P 66549-42-6P 92148-77-1P 117278-79-2P 136912-43-1P 136912-45-3P 136912-47-5P 152342-93-3P 159800-46-1P 159800-47-2P 159800-64-3P 159800-67-6P 159800-68-7P 159800-72-3P 199166-20-6P
- RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)
- IT 57-83-0, Progestin, biological studies
- RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(agonists; 1-(Arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines)
- IT 159800-21-2P
- RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(1-(arylsulfonyl)-, 1-(arylcarbonyl)-, and 1-(arylphosphonyl)-3-phenyl-1,4,5,6-tetrahydropyridazines as progestin agonists)
- RN 159800-21-2 HCAPLUS
- CN Pyridazine, 3-(3,4-dichlorophenyl)-1,4,5,6-tetrahydro-1-(2-thienylcarbonyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 21 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:476806 HCAPLUS Full-text

DOCUMENT NUMBER: 125:142755

TITLE: Pyridazinoquinoline compounds

INVENTOR(S): Bare, Thomas Michael; Chapdelaine, Marc Jerome; Davenport, Timothy Wayne; Empfield, James Roy; Garcia-Davenport, Laura Enid; Jackson, Paul Francis; McKinney, Jeffrey Alan; McLaren, Charles David;

PATENT ASSIGNEE(S): Sparks, Richard Bruce  
 SOURCE: Zeneca Limited, UK  
 PCT Int. Appl., 214 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9615127	A1	19960523	WO 1995-GB2613	19951108 <--
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2202135	A1	19960523	CA 1995-2202135	19951108 <--
AU 9538132	A	19960606	AU 1995-38132	19951108 <--
AU 705938	B2	19990603		
EP 790996	A1	19970827	EP 1995-936046	19951108 <--
EP 790996	B1	20020327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1171787	A	19980128	CN 1995-197220	19951108 <--
CN 1067685	B	20010627		
JP 10508617	T	19980825	JP 1995-515817	19951108 <--
AT 215085	T	20020415	AT 1995-936046	19951108 <--
FI 9701971	A	19970512	FI 1997-1971	19970507 <--
NO 9702153	A	19970709	NO 1997-2153	19970509 <--
NO 308899	B1	20001113		
US 6214826	B1	20010410	US 1999-365562	19990802 <--
PRIORITY APPLN. INFO.:				
			GB 1994-22894	A 19941112 <--
			WO 1995-GB2613	W 19951108 <--
			US 1997-836082	B1 19970502 <--
			US 1998-128038	B1 19980803 <--

OTHER SOURCE(S): MARPAT 125:142755

ED Entered STN: 13 Aug 1996

AB Pyridazinoquinolines and related compds. I [ring A is an orthofused aromatic or heteroarom. five- or six-membered ring; R = halo, C1-C4 alkyl, NO<sub>2</sub>, CN, etc.; R<sub>1</sub> = H, C1-C6 alkyl, (CH<sub>2</sub>)<sub>n</sub>L, where n = 0-6, L = (un)substituted aryl or heteroaryl or n > 0, L = OH, OAc, halo, CF<sub>3</sub>, etc.; R<sub>2</sub> = H, (CH<sub>2</sub>)<sub>n</sub>L; R<sub>3</sub> = H, acyl, alkyl, etc.; R<sub>4n</sub> = bond or H<sub>2</sub>; R<sub>5</sub> = H, C1-C6-alkyl or alkylaryl] or pharmaceutical compns. containing them were prepared for the treatment of neurol. disorders. Thus, di-Me 7-chloro-4-hydroxy-2,3-quinolinedicarboxylate was reacted with 2-hydroxyethylhydrazine and the mixture treated with N-methylglucamine to afford 37% 7-chloro-1-hydroxy-3-(2-hydroxyethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione. The quinolinedicarboxylate substrate was prepared from Me 2-amino-4-chlorobenzoate and di-Me acetylenedicarboxylate. Compds. I reduced ischemic damage, e.g., 7-chloro-4-hydroxy-5,10-dihydro-2-p-tolylpyridazino[4,5-b]quinolin-1-one at an i.v. dose of 10 mg/kg/h caused an infarct % volume change of -42% while a 5.0 mg/kg/h i.v. dosage caused a -8% reduction

IC ICM C07D471-04

ICS A61K031-435; C07D471-14; C07D491-147; C07D495-14

ICI C07D471-04, C07D237-00, C07D221-00

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1

ST pyridazinoquinoline aryl prepn treatment neurol disorder; stroke

treatment pyridazinoquinoline; quinoline pyridazino  
 prepn treatment neurol disorder

IT Brain, disease  
 (stroke, preparation of pyridazinoquinolines)

IT 179543-41-0P 179543-45-4P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of pyridazinoquinolines)

IT 179543-44-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation of pyridazinoquinolines)

IT 79-03-8, Propionyl chloride 92-54-6, n-Phenylpiperazine 100-52-7, Benzaldehyde, reactions 100-63-0, Phenylhydrazine 102-50-1, 4-Methoxy-2-methylaniline 109-84-2, 2-Hydroxyethylhydrazine 123-75-1, Pyrrolidine, reactions 156-51-4, Phenethylhydrazine sulfate 446-48-0, 2-Fluorobenzyl bromide 615-00-9, 2,4-Dimethylphenylhydrazine 622-88-8, 4-Bromophenylhydrazine hydrochloride 637-60-5, 4-Methylphenylhydrazine hydrochloride 762-42-5, Dimethyl acetylenedicarboxylate 823-85-8, 4-Fluorophenylhydrazine hydrochloride 870-46-2, tert-Butyl carbazate 1073-69-4, 4-Chlorophenylhydrazine 1074-82-4, Potassium phthalimide 1490-25-1, Carbomethoxypropionyl chloride 2243-56-3, 1-Naphthylhydrazine hydrochloride 5900-58-3, Methyl 2-amino-4-chlorobenzoate 6284-40-8, n-Methylglucamine 6329-90-4, 3-Chloro-p-anisidine hydrochloride 6628-77-9, 5-Amino-2-methoxypyridine 13123-92-7, 2,4-Dichlorophenylhydrazine 16726-41-3 19501-58-7, 4-Methoxyphenylhydrazine hydrochloride 19690-59-6 20570-96-1, Benzylhydrazine dihydrochloride 39232-91-2, 3-Methoxyphenylhydrazine hydrochloride 51145-58-5, 4-Benzoyloxyphenylhydrazine 57396-67-5, 2-Methoxyphenylhydrazine hydrochloride 58791-94-9 63756-98-9, 3,4-Dimethoxyphenylhydrazine 147494-03-9 147494-49-3 170142-20-8 170143-20-1 170143-35-8 170143-39-2 170143-43-8 170143-56-3 170143-57-4 170143-58-5 170143-59-6  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of pyridazinoquinolines)

IT 24630-85-1P, 3-Chloro-4-methoxyphenylhydrazine 93048-16-9P  
 133115-72-7P, 4-(Trifluoromethoxy)phenylhydrazine hydrochloride  
 147494-01-7P 160664-95-9P, 5-Hydrazino-2-methoxypyridine 170141-82-9P  
 170141-88-5P 170141-89-6P 170142-01-5P 170142-12-8P 170142-26-4P  
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 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of pyridazinoquinolines)

IT 170141-81-8P 170141-83-0P 170141-84-1P 170141-86-3P 170141-87-4P  
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10/518,503

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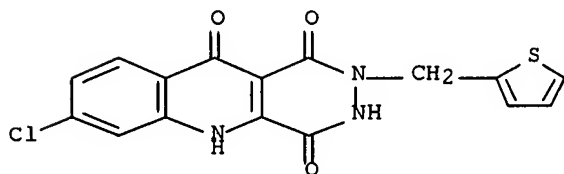
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of pyridazinoquinolines)

IT 170142-52-6P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of pyridazinoquinolines)

RN 170142-52-6 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 7-chloro-2,3-dihydro-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 22 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:685324 HCAPLUS Full-text

DOCUMENT NUMBER: 125:328724

TITLE: Preparation of dihydropyridazinones and pyridazinones as fungicides and insecticides

INVENTOR(S): Ross, Ronald; Shaber, Steven Howard; Szapacs, Edward Michael

PATENT ASSIGNEE(S): Rohm and Haas Company, USA

SOURCE: Eur. Pat. Appl., 25 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 738716	A2	19961023	EP 1996-302488	19960409 <--
EP 738716	A3	19981230		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
US 5635494	A	19970603	US 1995-426514	19950421 <--
AU 9650550	A	19961031	AU 1996-50550	19960409 <--
AU 713334	B2	19991202		
CA 2174296	A1	19961022	CA 1996-2174296	19960416 <--
TW 499294	B	20020821	TW 1996-85104563	19960417 <--
ZA 9603140	A	19961021	ZA 1996-3140	19960419 <--
JP 08291147	A	19961105	JP 1996-120852	19960419 <--
CN 1143637	A	19970226	CN 1996-104596	19960419 <--
CN 1124267	B	20031015		
HU 9601035	A2	19970428	HU 1996-1035	19960419 <--
BR 9602004	A	19980407	BR 1996-2004	19960419 <--
PRIORITY APPLN. INFO.:			US 1995-426514	A 19950421 <--

OTHER SOURCE(S): MARPAT 125:328724

ED Entered STN: 21 Nov 1996

AB The title compds. [I; W = CH3OA:CC(O)VCH3 (wherein A = N, CH; V = O, NH); X = H, halo, C1-4 alkyl, etc.; Y = O, S, (substituted) NH, etc.; R1 = H, C1-12 alkyl, C1-12 alkoxy, etc.; R2, R3 = H, halo, C1-8 alkyl, etc.; n = 0-1] having fungicidal and insecticidal properties, were prepared Thus, reaction of 6-(3-hydroxyphenyl)-2-(2',2'2'trifluoroethyl)-3(2H)- pyridazinone with Me  $\alpha$ -(2-bromomethylphenyl)- $\beta$ - methoxyacrylate in the presence of KOH in DMF afforded the expected pyridazinone II which showed 90% or better control when tested against Mexican bean beetle and two-spotted spider mite at 300 g/ha.

IC ICM C07D237-16

ICS C07D237-18; C07D237-20; C07D237-22; A01N043-58

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 5

ST pyridazinone prepn fungicide agrochem insecticide;hydroxypyridazinone prepn fungicide agrochem insecticide

IT Insecticides

(preparation of dihydropyridazinones and pyridazinones as fungicides and insecticides)

IT Fungicides and Fungistats

(agrochem., preparation of dihydropyridazinones and pyridazinones as fungicides and insecticides)

IT	183233-06-9P	183233-08-1P	183233-09-2P	183233-10-5P	183233-12-7P
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	183233-21-8P	183233-23-0P	183233-24-1P	183233-26-3P	183233-27-4P
	183233-28-5P	183233-29-6P	183233-30-9P	183233-31-0P	183233-32-1P
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	183233-39-8P	183233-40-1P	183233-41-2P	183233-42-3P	183233-43-4P
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	183233-53-6P	183233-54-7P	183233-55-8P	183233-56-9P	183233-57-0P
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	183233-69-4P	183233-70-7P	183233-71-8P	183233-72-9P	183233-73-0P
	183233-74-1P	183233-75-2P	183233-77-4P		

RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of dihydropyridazinones and pyridazinones as fungicides and insecticides)

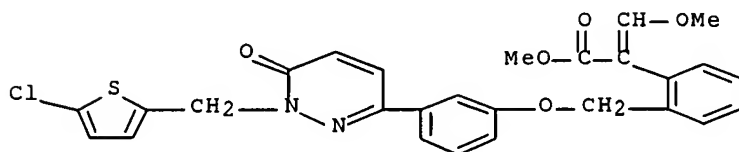
IT 100-39-0, Benzyl bromide 106-94-5, Propyl bromide 108-46-3,  
Resorcinol, reactions 121-71-1, 3'-Hydroxyacetophenone 141-30-0, 3,6-  
Dichloropyridazine 298-12-4, Glyoxylic acid 107048-59-9  
183233-83-2  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of dihydropyridazinones and pyridazinones  
as fungicides and insecticides)

IT 147849-75-0P 183233-79-6P 183233-80-9P 183233-81-0P 183233-82-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation of dihydropyridazinones and pyridazinones  
as fungicides and insecticides)

IT 183233-44-5P  
RL: AGR (Agricultural use); BAC (Biological activity or effector, except  
adverse); BSU (Biological study, unclassified); SPN (Synthetic  
preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of dihydropyridazinones and pyridazinones  
as fungicides and insecticides)

RN 183233-44-5 HCAPLUS

CN Benzeneacetic acid, 2-[[3-[1-[(5-chloro-2-thienyl)methyl]-1,6-dihydro-6-  
oxo-3-pyridazinyl]phenoxy]methyl]- $\alpha$ -(methoxymethylene)-, methyl  
ester (9CI) (CA INDEX NAME)



L99 ANSWER 23 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1995:909365 HCAPLUS Full-text  
DOCUMENT NUMBER: 123:313994  
TITLE: Preparation of pyridazinoquinolines as NMDA  
receptor antagonists  
INVENTOR(S): Bare, Thomas Michael; Sparks, Richard Bruce; Empfield,  
James Roy; Davenport, Timothy Wayne; McKinney, Jeffrey  
Alan  
PATENT ASSIGNEE(S): Zeneca Ltd., UK  
SOURCE: PCT Int. Appl., 185 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9511244	A1	19950427	WO 1994-GB2295	19941020 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, NL, NO, NZ, PL, PT, RO, RU, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				

10/518,503

IL 111266	A	20020310	IL 1994-111266	19941012 <--
ZA 9408178	A	19950424	ZA 1994-8178	19941018 <--
CA 2171332	A1	19950427	CA 1994-2171332	19941020 <--
AU 9479440	A	19950508	AU 1994-79440	19941020 <--
AU 688393	B2	19980312		
EP 724583	A1	19960807	EP 1994-930275	19941020 <--
EP 724583	B1	20001213		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 74161	A2	19961128	HU 1996-889	19941020 <--
CN 1138332	A	19961218	CN 1994-194578	19941020 <--
CN 1053189	B	20000607		
JP 09504519	T	19970506	JP 1995-511521	19941020 <--
JP 3583132	B2	20041027		
NZ 329303	A	20000128	NZ 1994-329303	19941020 <--
EP 1004582	A2	20000531	EP 2000-101917	19941020 <--
EP 1004582	A3	20000830		
EP 1004582	B1	20050518		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT

AT 198072	T	20001215	AT 1994-930275	19941020 <--
PL 180679	B1	20010330	PL 1994-314041	19941020 <--
PT 724583	T	20010330	PT 1994-930275	19941020 <--
ES 2154686	T3	20010416	ES 1994-930275	19941020 <--
RU 2168511	C2	20010610	RU 1996-109470	19941020 <--
SK 282491	B6	20020205	SK 1996-504	19941020 <--
SG 92630	A1	20021119	SG 1999-943	19941020 <--
CZ 292311	B6	20030917	CZ 1996-1138	19941020 <--
AT 295846	T	20050615	AT 2000-101917	19941020 <--
PT 1004582	T	20050930	PT 2000-101917	19941020 <--
ES 2241513	T3	20051101	ES 2000-101917	19941020 <--
RU 2279432	C2	20060710	RU 2001-103922	19941020 <--
TW 406082	B	20000921	TW 1994-83110721	19941118 <--
US 5744471	A	19980428	US 1996-637641	19960417 <--
FI 9601696	A	19960418	FI 1996-1696	19960418 <--
FI 113865	B1	20040630		
NO 9601584	A	19960419	NO 1996-1584	19960419 <--
NO 306995	B1	20000124		
FI 9700907	A	19970303	FI 1997-907	19970303 <--
FI 114916	B1	20050131		
US 6232313	B1	20010515	US 1998-44109	19980319 <--
AU 9868999	A	19980730	AU 1998-68999	19980527 <--
AU 721139	B2	20000622		
HK 1013997	A1	20020215	HK 1998-115415	19981224 <--
US 6103721	A	20000815	US 1999-455096	19991206 <--
GR 3035080	T3	20010330	GR 2000-402690	20001214 <--

PRIORITY APPLN. INFO.:

GB 1993-21854	A	19931022 <--
GB 1994-17171	A	19940825 <--
AU 1994-79440	A	19941020 <--
EP 1994-930275	A3	19941020 <--
RU 1996-109470	A3	19941020 <--
WO 1994-GB2295	W	19941020 <--
US 1996-637641	A3	19960417 <--
FI 1996-1696	A	19960418 <--
US 1998-44109	A3	19980319 <--

OTHER SOURCE(S): MARPAT 123:313994

ED Entered STN: 11 Nov 1995

AB Title compds. [(tautomeric) I; A = atoms to complete an (un)substituted benzene, pyridine, furan, pyrrole, or thiophene ring; R1,R2 = H, (CH2)nR; R = (un)substituted Ph, -heterocyclyl, -heteroaryl, OH, alkoxy, acyloxy, (di)alkylamino, etc.; R4 = 1 or more halo, alkyl, cyano, alkoxy, etc.; Z = O,

S, NH] were prepared Thus, Me 4-chloroanthranilate was cyclocondensed with MeO<sub>2</sub>CC.tplbond.CCO<sub>2</sub>Me and the product cyclocondensed in 2 steps with H<sub>2</sub>NNHCH<sub>2</sub>CH<sub>2</sub>OH to give title compound II (R = OH) which was converted in 2 steps to II (R = phthalimido). II [R = C<sub>6</sub>H<sub>4</sub>(OMe)-4] gave 80% protection from brain ischemic damage in carotid artery clip-occluded gerbils at 10mg/kg i.p.

IC ICM C07D471-04  
ICS A61K031-50  
ICI C07D471-04, C07D237-00, C07D221-00  
CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1  
ST pyridazinoquinoline prepn NMDA receptor antagonist  
IT Anticonvulsants and Antiepileptics  
(preparation of pyridazinoquinolines as NMDA receptor antagonists)  
IT Ischemia  
(treatment; preparation of pyridazinoquinolines as NMDA receptor antagonists)  
IT Nervous system  
(disease, degeneration, treatment; preparation of pyridazinoquinolines as NMDA receptor antagonists)  
IT Neurotransmitter antagonists  
(excitatory amino acid, preparation of pyridazinoquinolines as NMDA receptor antagonists)  
IT Neurotransmitter antagonists  
(methyl-D-aspartate, pyridazinoquinolines)  
IT Brain, disease  
(stroke, treatment; preparation of pyridazinoquinolines as NMDA receptor antagonists)  
IT 147494-01-7P. 170141-81-8P 170141-82-9P 170141-84-1P 170141-86-3P  
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170142-66-2P 170142-67-3P 170142-68-4P 170142-69-5P 170142-70-8P  
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170142-76-4P 170142-77-5P 170142-78-6P 170142-79-7P 170142-80-0P  
170142-81-1P 170142-82-2P 170142-83-3P 170142-84-4P 170142-85-5P  
170142-86-6P 170142-87-7P 170142-88-8P 170142-89-9P 170142-90-2P  
170142-91-3P 170142-92-4P 170142-93-5P 170142-94-6P 170142-95-7P  
170142-96-8P 170142-97-9P 170142-98-0P 170142-99-1P 170143-00-7P  
170143-01-8P 170143-02-9P 170143-03-0P 170143-04-1P 170143-05-2P  
170143-06-3P 170143-07-4P 170143-08-5P 170143-09-6P 170143-10-9P  
170143-11-0P 170143-12-1P 170143-13-2P 170143-14-3P 170143-15-4P  
170143-16-5P 170143-17-6P 170143-18-7P 170143-19-8P 170143-20-1P  
170143-21-2P 170143-22-3P 170143-23-4P 179543-33-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of pyridazinoquinolines as NMDA receptor antagonists)

IT 170141-83-0

RL: PRP (Properties)

(preparation of pyridazinoquinolines as NMDA receptor antagonists)

IT 92-54-6, N-Phenylpiperazine 100-52-7, Benzaldehyde, reactions  
 100-63-0, Phenylhydrazine 102-50-1, 2-Methyl-4-methoxyaniline  
 104-94-9, p-Anisidine 123-75-1, Pyrrolidine, reactions 156-51-4,  
 2-Phenethylhydrazine sulfate 446-48-0, 2-Fluorobenzyl bromide  
 615-00-9, 2,4-Dimethylphenylhydrazine 762-42-5, Dimethyl  
 acetylenedicarboxylate 1073-69-4, 4-Chlorophenylhydrazine 1074-82-4,  
 Potassium phthalimide 2243-56-3 5839-88-3, 4,4-Dimethyloxazoline-2,5-  
 dione 5900-58-3, Methyl 2-amino-4-chlorobenzoate 6329-90-4,  
 3-Chloro-p-anisidine hydrochloride 6628-77-9, 5-Amino-2-methoxypyridine  
 13123-92-7, 2,4-Dichlorophenylhydrazine 20570-96-1 24424-99-5,  
 Di-tert-butyl dicarbonate 35467-65-3, 4-Methylphenylhydrazine  
 hydrochloride 40594-35-2, 4-Fluorophenylhydrazine hydrochloride  
 41931-18-4, 4-Bromophenylhydrazine hydrochloride 51145-58-5,  
 4-Benzyloxyphenylhydrazine 57396-67-5, 2-Methoxyphenylhydrazine  
 hydrochloride 57396-68-6, 3-Methoxyphenylhydrazine hydrochloride  
 58791-94-9 63756-98-9, 3,4-Dimethoxyphenylhydrazine 70672-74-1,  
 4-Methoxyphenylhydrazine hydrochloride 118427-29-5, 4-  
 Isopropylphenylhydrazine hydrochloride 133115-72-7, 4-  
 (Trifluoromethoxy)phenylhydrazine hydrochloride 147494-03-9  
 147494-49-3 170143-56-3 170143-57-4 170143-58-5 170143-59-6  
 170143-60-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyridazinoquinolines as NMDA receptor antagonists)

IT 13957-54-5P 24630-85-1P, 3-Chloro-4-methoxyphenylhydrazine  
 93048-16-9P, 2-Methyl-4-methoxyphenylhydrazine hydrochloride  
 160664-95-9P, 5-Hydrazino-2-methoxypyridine 170143-24-5P 170143-25-6P  
 170143-26-7P 170143-27-8P 170143-28-9P 170143-29-0P 170143-30-3P  
 170143-31-4P 170143-32-5P 170143-33-6P 170143-34-7P 170143-35-8P  
 170143-36-9P 170143-37-0P 170143-38-1P 170143-41-6P 170143-42-7P  
 170143-43-8P 170143-44-9P 170143-45-0P 170143-47-2P 170143-48-3P  
 170143-49-4P 170143-50-7P 170143-51-8P 170143-52-9P 170143-53-0P  
 170143-54-1P 170143-55-2P 170143-61-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

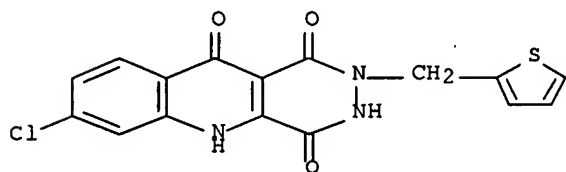
(preparation of pyridazinoquinolines as NMDA receptor antagonists)IT 170142-52-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of pyridazinoquinolines as NMDA receptor antagonists)

RN 170142-52-6 HCAPLUS

CN Pyridazino[4,5-b]quinoline-1,4,10(5H)-trione, 7-chloro-2,3-dihydro-2-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 24 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:52662 HCAPLUS

DOCUMENT NUMBER: 124:176127

TITLE: Preparation of sulfamoylindanyl- and  
sulfamoyl-1,2,3,4-tetrahydronaphthylpyridazinone\*  
\*\* derivatives as drugsINVENTOR(S): Ishida, Akihiko; Pponma, Koichi; Kono, Haruyuki;  
Tamura, Koji; Sasaki, YasuhikoPATENT ASSIGNEE(S): Tanabe Seiyaku Co, JapanSOURCE: Japan Kokai Tokkyo Koho, 35 pp.

CODEN: JKXXAF

DOCUMENT TYPE: PatentLANGUAGE: JapaneseFAMILY ACC. NUM. COUNT: 1PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07233072	A	19950905	JP 1994-322942	19941226 <--
PRIORITY APPLN. INFO.:			JP 1994-322942	A 19941226 <--
			JP 1993-333966	19931228 <--

OTHER SOURCE(S): MARPAT 124:176127

ED Entered STN: 26 Jan 1996

AB The title compds. [I; R1 = (un)substituted C1-10 alkyl, C3-6 cycloalkyl, lower alkenyl, (un)substituted heterocyclyl containing N, O, or S heteroatom, camphor-10-yl; R3 = H, (un)substituted lower alkyl, lower alkenyl; or R1 and R3 are linked to each other at the termini to form a lower alkylene; R2 = H, (un)substituted lower alkyl, aryl, lower alkenyl; A-B = ethylene or vinylene optionally substituted by 1-2 groups selected from lower alkyl or Ph; n = 1,2; D = H, halo], which are useful for the treatment and prevention of nephritis, in particular glomerulonephritis, IgA nephritis, nephrotic syndrome, and/or lupus nephritis and as blood platelet aggregation inhibitors and/or protective agents against endotoxin shock, are prepared Thus, 1.15 g 2-amino-5-[3-oxo-3(H)-4,5-dihydropyridazin-6-yl]indan was dissolved in EtOAc and THF, followed by successively adding an aqueous solution of 1.4 g K<sub>2</sub>CO<sub>3</sub> in 20 mL and 0.57 g MeSO<sub>2</sub>Cl, and the resulting mixture was stirred for 2 h to give 1.08 g 2-methanesulfonylamino-5-[3-oxo-3(H)-4,5-dihydropyridazin -6-yl]indan (II). Mice was administered with II at 100 mg/kg p.o. and after 30 min treated with a solution of Escherichia coli-derived endotoxin (lipopolysaccharides) in physiol. saline at 100 mg/10 mL/kg i.p. The survival ratio of the treated mice was 100 %.

IC ICM A61K031-50

ICS A61K031-50; C07D237-04; C07D401-12; C07D403-12; C07D409-12;  
C07D409-14; C07D413-12; C07D417-14ICI C07D401-12, C07D213-16, C07D237-04; C07D401-12, C07D215-04, C07D237-04;  
C07D409-12, C07D237-04, C07D333-10; C07D409-14, C07D213-16CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

ST sulfamoylindanylpyridazinone prepn treatment nephritis;  
sulfamoyltetrahydronaphthylpyridazinone prepn treatment nephrotic  
syndrome; glomerulonephritis treatment sulfamoylindanylpyridazinone\*\*  
\* ; IgA nephritis treatment \*\*\*sulfamoylindanylpyridazinone; lupus  
nephritis treatment sulfamoylindanylpyridazinone; blood platelet  
aggregation inhibitor sulfamoylindanylpyridazinone; endotoxin  
shock protection sulfamoylindanylpyridazinone;  
indanylpyridazinone sulfamoyl prepn treatment nephritis;  
naphthylpyridazinone sulfamoyl prepn treatment nephrotic syndrome;  
pyridazinone sulfamoyl indanyl prepn treatment nephritis

IT Blood platelet aggregation inhibitors  
(preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyridazinone derivs. as drugs)

IT Shock  
(endotoxin, preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyridazinone derivs. as drugs for treating nephritis and protecting against endotoxin shock)

IT Kidney, disease  
(nephritis, preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyridazinone derivs. as drugs for treating nephritis (glomerulonephritis, IgA nephritis, nephrotic syndrome, and/or lupus nephritis))

IT	155718-08-4P	155718-25-5P	155718-33-5P	155718-34-6P	155718-80-2P
	155719-82-7P	172679-62-8P	172679-63-9P	172679-64-0P	172679-65-1P
	172679-66-2P	172679-67-3P	172679-68-4P	172679-69-5P	172679-70-8P
	172679-71-9P	172679-72-0P	172679-73-1P	172679-74-2P	172679-75-3P
	172679-76-4P	172679-77-5P	172679-78-6P	172679-79-7P	172679-80-0P
	172679-81-1P	172679-82-2P	172679-83-3P	172679-84-4P	172679-85-5P
	172679-86-6P	172679-87-7P	172679-88-8P	172679-89-9P	172679-90-2P
	172679-91-3P	172679-92-4P	172679-93-5P	172679-94-6P	172679-95-7P
	172679-96-8P	172679-97-9P	172679-99-1P	172680-00-1P	172680-01-2P
	172680-02-3P	172680-03-4P	172680-04-5P	172680-05-6P	172680-06-7P
	172680-07-8P	172680-08-9P	172680-09-0P	172680-10-3P	172680-11-4P
	172680-12-5P	172680-13-6P	172680-14-7P	172680-15-8P	172680-16-9P
	172680-17-0P	172680-18-1P	172680-19-2P	172680-20-5P	172680-21-6P
	172680-22-7P	172680-23-8P	172680-24-9P	172680-25-0P	172680-26-1P
	172680-27-2P	172680-28-3P	172680-29-4P	172680-30-7P	172680-31-8P
	172680-32-9P	172680-33-0P	172680-34-1P	172680-35-2P	172680-36-3P
	172680-37-4P	172680-38-5P	172680-39-6P	172680-40-9P	172680-41-0P
	172680-42-1P	172680-43-2P	172680-44-3P	172680-45-4P	172680-46-5P
	<u>172680-47-6P</u>	172680-48-7P	172680-49-8P	172680-50-1P	
	172680-51-2P	172680-52-3P	172680-53-4P	172680-54-5P	172680-55-6P
	172680-56-7P	172680-57-8P	172680-58-9P	172680-59-0P	172680-60-3P
	172680-61-4P	172680-62-5P	172680-63-6P	172680-64-7P	172680-65-8P
	172680-66-9P	172680-67-0P	172680-68-1P	172680-69-2P	172680-70-5P
	172680-71-6P	172680-72-7P	172680-73-8P	172680-74-9P	172680-75-0P
	172680-76-1P				

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyridazinone derivs. as drugs)

IT 74-88-4, Methyl iodide, reactions 75-36-5, Acetyl chloride 75-86-5, Acetone cyanohydrin 79-30-1, 2-Methylpropanoyl chloride 85-44-9, Phthalic anhydride 96-32-2, Methyl bromoacetate 100-39-0, Benzyl bromide 100-52-7, Benzaldehyde, reactions 103-80-0, Phenylacetyl chloride 105-36-2, Ethyl bromoacetate 106-65-0, Dimethyl succinate 107-08-4, Propyl iodide 107-99-3, 2-Dimethylaminoethyl chloride 108-30-5, Succinic anhydride, reactions 108-90-7, Chlorobenzene, reactions 123-38-6, Propanal, reactions 124-63-0, Methanesulfonyl chloride 677-25-8, Vinylsulfonyl fluoride 1490-25-1, Methyl succinyl chloride 1622-32-8, 2-Chloroethanesulfonyl chloride 1633-82-5, 3-Chloropropanesulfonyl chloride 2386-60-9, n-Butanesulfonyl chloride 2975-41-9, 2-Aminoindan 3099-31-8, 3-Picolyl chloride 3144-16-9, (+)-Camphorsulfonic acid 3878-55-5, Methyl hydrogen succinate 7803-57-8, Hydrazine hydrate 10147-36-1, Propanesulfonyl chloride 16629-19-9, 2-Thiophenesulfonyl chloride 79686-90-1, 2-Methoxycarbonylamino succinic anhydride 114149-01-8 138006-38-9, 2-Propionylaminoindan 166978-75-2 172679-98-0 172680-84-1 172681-01-5

RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyrida  
zinone derivs. as drugs)

IT 31952-21-3P 64624-93-7P, 2-Propylindan 155719-25-8P,  
2-Butanesulfonylaminoindan 155719-33-8P 155719-35-0P 155719-36-1P  
155719-37-2P 155719-41-8P 155719-43-0P 155719-53-2P 155719-54-3P  
166978-76-3P 166978-77-4P 166978-78-5P 166978-83-2P 166978-84-3P  
166978-85-4P 172680-79-4P 172680-80-7P 172680-81-8P 172680-82-9P  
172680-83-0P 172680-85-2P 172680-86-3P 172680-87-4P 172680-88-5P  
172680-89-6P 172680-90-9P 172680-91-0P 172680-92-1P 172680-93-2P  
172680-94-3P 172680-95-4P 172680-96-5P 172680-97-6P 172680-98-7P  
172680-99-8P 172681-00-4P 172681-02-6P 172681-03-7P 172681-04-8P  
172681-05-9P

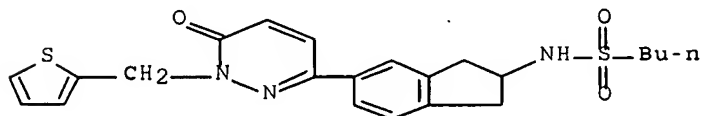
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyrida  
zinone derivs. as drugs)

IT 172680-47-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of sulfamoylindanyl- and sulfamoyltetrahydronaphthylpyrida  
zinone derivs. as drugs)

RN 172680-47-6 HCAPLUS

CN 1-Butanesulfonamide, N-[5-[1,6-dihydro-6-oxo-1-(2-thienylmethyl)-3-  
pyridazinyl]-2,3-dihydro-1H-inden-2-yl]- (9CI) (CA INDEX NAME)



L99 ANSWER 25 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:257968 HCAPLUS Full-text

DOCUMENT NUMBER: 122:31542

TITLE: Preparation of 1-arylsulfonyl, arylcabonyl and  
1-arylphosphonyl-3-phenyl-1,4,5,6-  
tetrahydropyridazine progestin agonists

INVENTOR(S): Combs, Donald W.

PATENT ASSIGNEE(S): Ortho Pharma Corp., USA

SOURCE: PCT Int. Appl., 73 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9401412	A1	19940120	WO 1993-US6394	19930701 <--
W:	AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SE, SK, UA			
RW:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, BG, CI, CM, GA, GN			
AU 9346670	A	19940131	AU 1993-46670	19930701 <--

AU 668206	B2	19960426		
EP 650480	A1	19950503	EP 1993-917006	19930701 <--
EP 650480	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
HU 68424	A2	19950628	HU 1994-3841	19930701 <--
JP 07508987	T	19951005	JP 1993-503486	19930701 <--
BR 9306661	A	19981208	BR 1993-6661	19930701 <--
AT 209189	T	20011215	AT 1993-917006	19930701 <--
PT 650480	T	20020328	PT 1993-917006	19930701 <--
ES 2168276	T3	20020616	ES 1993-917006	19930701 <--
US 5684151	A	19971104	US 1995-362476	19950306 <--
PRIORITY APPLN. INFO.:			US 1992-906984	A2 19920701 <--
			US 1993-80986	A2 19930621 <--
			WO 1993-US6394	W 19930701 <--

OTHER SOURCE(S): MARPAT 122:31542

ED Entered STN: 22 Dec 1994

AB The title compds. [I; A = Q1, Q2; R1 = halogen, CF3, NO2; R3 = H, Cl-6 (un)branched alkyl, halogen, CF3; R5 = H, Me; W = direct bond, CH:CH; R1R1 = CH:CHCH:CH], useful as contraceptives and in the treatment of osteoporosis, and which bind to the GABAA receptor, are prepared. Thus, tetrahydropyridazine II (m.p. 148-149°) was prepared and demonstrated a IC50 (i.e., binding affinity for the rabbit uterus progestin receptor) of 5.3 nM.

IC C07D237-04; C07D409-04; C07F096-509; A61K031-50

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1, 63

ST arylphosphonylphenyltetrahydropyridazine prepn progestin agonist; osteoporosis treatment prepn arylphosphonylphenyltetrahydropyridazine; GABA receptor binding arylphosphonylphenyltetrahydropyridazine; arylsulfonylphenyltetrahydropyridazine progestin agonist; contraceptive prepn arylsulfonylphenyltetrahydropyridazine\*\*  
\*

IT Osteoblast

(1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists for stimulation of)

IT Osteoporosis

(1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists for treatment of)

IT Contraceptives

(1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazines)

IT Progestogen receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine as agonists of)

IT Neurotransmitter agonists

Neurotransmitter antagonists

(GABAergicA, 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazines)

IT Receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(progestogen, preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine as agonists of)

IT	159797-68-9	159797-79-2	159797-89-4	159798-05-7	159798-06-8
	159798-07-9	159798-08-0	159798-43-3	159798-61-5	159798-69-3
	159798-78-4	159798-82-0	159798-88-6	159798-99-9	159799-45-8
	159799-87-8	159799-89-0	159799-91-4	159799-93-6	159799-98-1
	159800-01-8	159800-03-0	159800-33-6	159800-34-7	159800-35-8

159800-38-1 159800-39-2 159800-44-9 159800-45-0

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(claimed compound; preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists)

IT 57-83-0, Pregn-4-ene-3,20-dione, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine as agonists of)

IT 77-73-6, Dicyclopentadiene 95-13-6, Indene 98-61-3,  
 4-Iodobenzenesulfonyl chloride 98-88-4, Benzoyl chloride 108-30-5,  
 Succinic anhydride, reactions 378-77-8, Sodium pentafluoropropionate  
 527-69-5, 2-Furoyl chloride 532-27-4,  $\alpha$ -Chloroacetophenone  
 542-92-7, Cyclopentadiene, reactions 672-75-3, 3-Bromo-4-fluorobenzoyl  
 chloride 824-72-6, Phenylphosphonic dichloride 931-57-7,  
 1-Methoxycyclohexene 1003-09-4, 2-Bromothiophene 1576-35-8,  
 4-Toluenesulfonyl hydrazide 2751-27-1 3024-72-4, 3,4-Dichlorobenzoyl  
 chloride 3140-93-0, 2,3-Dibromothiophene 3984-34-7,  
 3-(4-Chlorobenzoyl)propionic acid 4083-64-1, Tosyl isocyanate  
 5271-67-0, 2-Thiophenecarbonyl chloride 6335-44-0 15988-11-1  
 18523-22-3, 2,3'-Dibromoacetophenone 52240-00-3 159797-68-9  
 159797-71-4 159798-04-6 159798-06-8 159798-97-7 159798-98-8  
 159799-02-7 159799-10-7 159799-11-8 159799-15-2 159799-45-8  
 159799-85-6 159800-18-7 159800-62-1 159800-64-3 159800-65-4  
 159800-69-8 159800-73-4 159800-74-5 159800-75-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine as progestin agonists)

IT 1011-46-7P 1017-06-7P 1079-73-8P 2166-13-4P 24734-44-9P  
 29681-94-5P 36725-34-5P 52239-89-1P 52239-91-5P 52239-99-3P  
 62903-37-1P 66548-93-4P 66549-42-6P 74190-69-5P 92148-77-1P  
 92244-97-8P 99070-42-5P 103853-58-3P 117278-79-2P 136912-43-1P  
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 159800-72-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine as progestin agonists)

IT 71094-17-2P 109809-47-4P 159797-68-9P 159797-69-0P 159797-70-3P  
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159798-86-4P	159798-87-5P	159798-88-6P	159798-89-7P	159798-90-0P
159798-91-1P	159798-92-2P	159798-93-3P	159798-94-4P	159798-95-5P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists)

IT	159799-99-2P	159800-00-7P	159800-01-8P	159800-02-9P	159800-03-0P
	159800-04-1P	159800-05-2P	159800-06-3P	159800-07-4P	159800-08-5P
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	159800-19-8P	159800-20-1P	<u>159800-21-2P</u>	159800-22-3P	
	159800-23-4P	159800-24-5P	159800-25-6P	159800-26-7P	159800-27-8P
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	159805-26-2P				

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists)

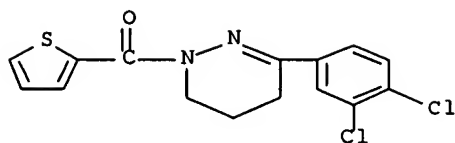
IT 159800-21-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1-arylsulfonyl, arylcabonyl and 1-arylphosphonyl-3-phenyl-1,4,5,6-tetrahydropyridazine progestin agonists)

RN 159800-21-2 HCAPLUS

CN Pyridazine, 3-(3,4-dichlorophenyl)-1,4,5,6-tetrahydro-1-(2-thienylcarbonyl)- (9CI) (CA INDEX NAME)



L99 ANSWER 26 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1992:531213 HCAPLUS Full-text  
 DOCUMENT NUMBER: 117:131213  
 TITLE: Preparation of dihydropyridazinones and related compounds as fungicides  
 INVENTOR(S): Egan, Anne Ritchie; Michelotti, Enrique Luis; Ross, Ronald, Jr.; Wilson, Willie Joe  
 PATENT ASSIGNEE(S): Rohm and Haas Co., USA  
 SOURCE: Eur. Pat. Appl., 85 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 478195	A1	19920401	EP 1991-308404	19910913 <--
EP 478195	B1	19990526		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 180475	T	19990615	AT 1991-308404	19910913 <--
ES 2131506	T3	19990801	ES 1991-308404	19910913 <--
CA 2051471	A1	19920322	CA 1991-2051471	19910916 <--
AU 9184602	A	19920326	AU 1991-84602	19910919 <--
AU 651375	B2	19940721		
ZA 9107466	A	19920527	ZA 1991-7466	19910919 <--
HU 59379	A2	19920528	HU 1991-3020	19910920 <--
BR 9104043	A	19920602	BR 1991-4043	19910920 <--
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JP 3166782	B2	20010514		
KR 204381	B1	19990615	KR 1991-16465	19910920 <--
IL 99542	A	20010111	IL 1991-99542	19910920 <--
JP 2001139553	A	20010522	JP 2000-341752	19910920 <--
JP 3408790	B2	20030519		
JP 2001181261	A	20010703	JP 2000-342924	19910920 <--
JP 3408791	B2	20030519		
CN 1069729	A	19930310	CN 1991-110000	19911028 <--
CN 1038249	B	19980506		
JP 05286944	A	19931102	JP 1992-62341	19920318 <--
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US 5552409	A	19960903	US 1994-221229	19940331 <--
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US 5726162	A	19980310	US 1996-741248	19961030 <--
US 5728698	A	19980317	US 1996-740548	19961030 <--
US 5728694	A	19980317	US 1996-740549	19961030 <--
US 5728715	A	19980317	US 1996-741249	19961030 <--
JP 2001172264	A	20010626	JP 2000-342863	20001110 <--
JP 3364205	B2	20030108		

## PRIORITY APPLN. INFO.:

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US 1991-749576	A 19910828 <--
JP 1991-241806	A3 19910920 <--
JP 1992-62341	A 19920318 <--
US 1994-221229	A3 19940331 <--
US 1995-467384	A3 19950606 <--

OTHER SOURCE(S): MARPAT 117:131213

ED Entered STN: 04 Oct 1992

AB Title compds. I [A = (CHR2)nCHR7Z, (CHR2)nOZ, (CHR2)nSZ, OCHR7Z, etc.; n = 0-2; D = N, CR2; Q = (substituted) Ph, -naphthyl, -styryl, -pyridyl, -quinolyl, -indolyl, etc.; Z = CO, C:S; R1 = (substituted) alkyl, -alkynyl, -alkenyl, Ph, etc.; R2 = H, C1-3 alkyl, Ph, halo; R7 = R2, alkenylalkenyl, alkynyl, dialkynyl, haloalkynyl, alkenylalkynyl; or R2 and R7 form fused Ph ring, etc., with provisos] were prepared as medical and agrochem. fungicides. Thus, 3-(4-chlorobenzoyl)propionic acid (preparation given) in absolute EtOH was refluxed for 3 h with hydrazine and the dihydropyridazinone formed was N-alkynylated by 1-bromopent-2-yne to give title compound II. II at 200 ppm gave 99% control of Pyricularia oryzae on rice and at 100 ppm gave 100% control of Candida albicans.

IC ICM C07D237-14

ICS C07D237-26; C07D409-04; C07D273-04; C07D213-26; C07D215-22; C07D243-02; C07D285-18; C07D401-04; C07D403-04; C07D403-06

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 5

ST pyridazinone dihydro prepn fungicide; medical agrochem fungicide  
dihydropyridazinone

IT Fungicides and Fungistats

(dihydropyridazinones and related compds.)

IT Fungicides and Fungistats

(agrochem., dihydropyridazinones and related compds.)

IT Fungicides and Fungistats

(synergistic, dihydropyridazinone-containing compns.)

IT 20072-61-1P	33347-86-3P	35507-89-2P	38958-82-6P	38958-84-8P
52239-79-9P	142027-09-6P	142027-10-9P	142027-11-0P	142027-12-1P
142027-13-2P	142027-14-3P	142027-15-4P	142027-16-5P	142027-17-6P
142027-18-7P	142027-19-8P	142027-20-1P	142027-21-2P	142027-22-3P
142027-23-4P	142027-24-5P	142027-25-6P	142027-26-7P	142027-27-8P
142027-28-9P	142027-29-0P	142027-30-3P	142027-31-4P	142027-32-5P
142027-33-6P	142027-34-7P	<u>142027-35-8P</u>	142027-36-9P	
142027-37-0P	142027-38-1P	142027-39-2P	142027-40-5P	142027-41-6P
142027-42-7P	142027-43-8P	142027-44-9P	142027-45-0P	142027-46-1P
142027-47-2P	142027-48-3P	142027-49-4P	142027-50-7P	142027-51-8P
142027-52-9P	142027-53-0P	142027-54-1P	142027-55-2P	142027-56-3P
142027-57-4P	142027-58-5P	142027-59-6P	142027-60-9P	142027-61-0P
142027-62-1P	142027-63-2P	142027-64-3P	142027-65-4P	142027-66-5P
142027-67-6P	142027-68-7P	142027-69-8P	142027-70-1P	142027-71-2P
142027-72-3P	142027-73-4P	142027-74-5P	142027-75-6P	142027-76-7P
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142028-02-2P	142028-03-3P	142028-04-4P	142028-05-5P	142028-06-6P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of, as fungicide)

IT 89-41-8P, 3-Nitro-4-methoxybenzoic acid 403-17-8P 664-66-4P  
 697-20-1P 765-50-4P, 2-Chloromethylthiophene 866-16-0P  
 1079-73-8P 1810-67-9P 2919-05-3P, 4-Penten-2-yn-1-ol 2927-72-2P  
 3355-28-0P, 1-Bromo-2-butyne 3984-34-7P 4653-13-8P 5381-29-3P  
 13280-03-0P 18350-44-2P 19927-64-1P 25445-82-3P 26673-31-4P  
 27956-39-4P 27993-56-2P, 4-Chloro- $\alpha$ -hydroxyacetophenone  
 35982-98-0P 41345-53-3P, 2,4-Pentadiyn-1-ol 42134-54-3P 50597-19-8P  
 50677-27-5P 52157-57-0P, 2-Chloromethyl-5-methylfuran 52240-20-7P  
 53691-91-1P 55631-84-0P 61493-85-4P 62903-05-3P 62903-14-4P  
 64244-47-9P 65738-56-9P 69676-55-7P 70391-14-9P 76053-43-5P  
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 142048-69-9P 142048-70-2P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as intermediate for fungicides)

IT 50-00-0, Formaldehyde, reactions 59-88-1, Phenylhydrazine hydrochloride  
 60-34-4, Methyl hydrazine 64-17-5, Ethanol, reactions 64-18-6, Formic acid, reactions  
 67-56-1, Methanol, reactions 68-12-2, reactions 74-96-4, Bromoethane 75-07-0, Acetaldehyde, reactions 75-21-8,  
 Oxirane, reactions 90-60-8, 3,5-Dichlorosalicylaldehyde 91-20-3, Naphthalene, reactions  
 93-10-7, 2-Quinolinecarboxylic acid 95-50-1, 1,2-Dichlorobenzene 96-32-2, Methyl bromoacetate 98-88-4,  
 Benzoylchloride 99-91-2 100-39-0, Benzyl bromide 102-92-1, Cinnamoyl chloride 104-88-1,  
 4-Chlorobenzaldehyde, reactions 105-36-2, Ethyl bromoacetate 106-47-8, 4-Chloroaniline,  
 reactions 106-65-0, Dimethyl succinate 106-96-7, Propargyl bromide 107-19-7, Propargyl alcohol  
 107-91-5, Cyanoacetamide 108-24-7, Acetic anhydride 108-30-5, Succinic anhydride, reactions  
 108-90-7, Chlorobenzene, reactions 109-50-2, 3-Hexyn-2-ol 109-69-3, Butyl chloride  
 110-65-6, 2-Butyne-1,4-diol 110-87-2, 3,4-Dihydro-2H-pyran 121-90-4, 3-Nitrobenzoyl chloride  
 122-01-0, 4-Chlorobenzoyl chloride 123-54-6, 2,4-Pentanedione, reactions 123-76-2  
 124-38-9, Carbon dioxide, reactions 124-63-0, Methanesulfonyl chloride 147-71-7,  
 D-Tartaric acid 298-12-4, Glyoxylic acid 302-01-2, Hydrazine, reactions 350-28-7  
 393-52-2, 2-Fluorobenzoyl chloride 455-86-7, 3,4-Difluorobenzoic acid 536-38-9  
 536-40-3 541-16-2, Di-tert-butyl malonate 541-41-3, Ethyl chloroformate 590-14-7,  
 1-Bromo-1-propene 590-17-0, Bromoacetonitrile 593-66-8, Vinyl iodide 598-23-2,  
 3-Methylbutyne 609-65-4, 2-Chlorobenzoyl chloride 616-38-6, Dimethylcarbonate  
 618-46-2, 3-Chlorobenzoyl chloride 624-65-7, Propargyl chloride 627-15-6, 1,3-Dibromo-1-propene  
 636-72-6, 2-Thiophenemethanol 637-87-6 689-97-4, Vinylacetylene 697-17-6  
 699-30-9, Perfluorosuccinic anhydride

764-01-2, 2-Butyn-1-ol 764-60-3, 2-Hexyn-1-ol 766-80-3, 3-Chlorobenzyl bromide 821-10-3, 1,4-Dichloro-2-butyne 917-92-0, 3,3-Dimethyl-1-butyne 931-48-6, Cyclohexylacetylene 933-88-0, 2-Methylbenzoyl chloride 1007-16-5, 3-Bromo-4-fluorobenzoic acid 1128-05-8 1461-22-9, Tributyltin chloride 1501-05-9, 4-Benzoylbutyric acid 1504-58-1, 3-Phenyl-2-propyn-1-ol 1711-05-3, 3-Methoxybenzoyl chloride 1711-06-4, 3-Methylbenzoyl chloride 1711-07-5, 3-Fluorobenzoyl chloride 1711-11-1, 3-Cyanobenzoyl chloride 1878-66-6, 4-Chlorophenylacetic acid 2166-13-4 2219-66-1, 1,4-Dibromo-2-butyne 2251-65-2, 3-Trifluoromethylbenzoyl chloride 2810-04-0, Ethyl 2-**thiophenecarboxylate** 2905-65-9, Methyl 3-chlorobenzoate 3437-95-4, 2-**Iodothiophene** 4100-80-5, Methyl succinic anhydride 4114-31-2, Ethyl carbazate 4117-14-0, 2-Decyn-1-ol 4468-82-0 4784-77-4, Crotyl bromide 5911-08-0, Chloromethylcyclopropane 6273-45-6 6945-92-2, Ethyl hydrazinoacetate hydrochloride 7151-68-0, 3-Methoxy-4-methylbenzoic acid 7400-27-3, tert-Butylhydrazine hydrochloride 10229-10-4, 3-Pentyn-1-ol 14496-35-6 16400-32-1, 1-Bromo-2-pentyne 17715-00-3 19788-37-5 21615-34-9, 2-Methoxybenzoyl chloride 32137-20-5, 4-Chloro-3-fluorobenzotrifluoride 32315-10-9, Triphosgene 37908-96-6, 3-Chloro-4-methoxybenzoic acid 38002-45-8, 1-Bromo-3-trimethylsilyl-2-propyne 40757-20-8 41715-02-0 42348-86-7 52323-98-5 54369-44-7 54745-92-5, 2-Quinoxalinecarbonyl chloride 60811-18-9 66248-97-3 81159-43-5 91085-56-2 142048-71-3 142048-72-4

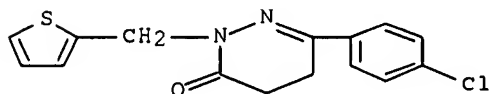
RL: RCT (Reactant); RACT (Reactant or reagent)  
(reaction of, in preparation of fungicides)

IT **142027-35-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(preparation of, as fungicide)

RN 142027-35-8 HCAPLUS

CN 3(2H)-Pyridazinone, 6-(4-chlorophenyl)-4,5-dihydro-2-(2-thienylmethyl)-(9CI) (CA INDEX NAME)



L99 ANSWER 27 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:656193 HCAPLUS Full-text

DOCUMENT NUMBER: 115:256193

TITLE: Preparation of fused **pyridazine** derivatives  
as thromboxane A2 (TXA2) synthetase inhibitors

INVENTOR(S): Ohi, Nobuhiro; Kuroki, Toshio; Yamaguchi, Masahisa;  
Akima, Michitaka; Koga, Takaki; Kamei, Kenshi

PATENT ASSIGNEE(S): Chugai Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 99 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9112251      A1      19910822      WO 1991-JP210      19910219 <--
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    LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT,
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AU 9172381      A      19910903      AU 1991-72381      19910219 <--
ZA 9101224      A      19911127      ZA 1991-1224      19910219 <--
JP 3120857      B2      20001225      JP 1991-504019    19910219 <--
PRIORITY APPLN. INFO.:      JP 1990-37966      A 19900219 <--
                                JP 1990-250934      A 19900920 <--
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                                WO 1991-JP210      A 19910219 <--

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OTHER SOURCE(S): MARPAT 115:256193

ED Entered STN: 14 Dec 1991

AB Title compds. [I; ring A = Q, or unsatd. 5- or 6-membered O-, N- or S-containing heterocycle, e.g. Q1, Q2; R1 = H, halo CO2H, alkoxycarbonyl, NO2, alkoxy; R2 = alkyl, cyclohexyl, (halo)benzyl, thienylmethyl, (halo or alkyl) unsatd. 5- or 6-membered heterocyclcyl containing 1-3 N atoms and/or 1 S atom, (un)substituted Ph; R3 = (un)substituted alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, cycloalkylmethyl, acyl, acylmethyl, PhSO2], useful as antiasthmatics and bronchodilators, are prepared Thus, a suspension of 4-phenyl-1-(2H)-phthalazinone 2.0, BrCH2CH2Br 5.5, K2CO3 7.5 g, and 60 mL DMF was stirred 2 h at 65° and thereto 4.3 g imidazole was added and the stirring was continued 5 h at 70° to give 0.5g a phthalazinone [II; R2 = Ph, R3 = 2-(1-imidazolyl)ethyl]. II (R2 = 3-pyridyl, R3 = 2-cyclohexylmethyl) in vitro inhibited 99% TXA2 in a test using rabbit blood platelets and porcine aorta microsomes and showed muscle relaxant activity in guinea pig trachea with -log[EC50] of 6.68. A total of 118 I were prepared and similarly tested.

IC ICM C07D401-04

ICS C07D401-14; C07D403-04; C07D403-06; C07D403-14; C07D405-04;  
C07D405-14; C07D409-04; C07D409-14; C07D417-04; C07D417-14;  
C07D471-04; C07D495-04; A61K031-50; C12N009-99

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1, 7

ST fused pyridazine prepn antiasthmatic; bronchodilator fused  
pyridazine; thromboxane A2 synthetase inhibitor; phthalazinone  
antiasthmatic bronchodilator; thienopyridazine antiasthmatic  
bronchodilator; pyridinopyridazinone antiasthmatic  
bronchodilator

IT Bronchodilators  
(phthalazinone, thienopyridazinone, and  
pyridopyridazinone derivs.)

IT Bronchodilators  
(antiasthmatics, phthalazinone, thienopyridazinone, and  
pyridopyridazinone derivs.)

IT 60832-04-4, Thromboxane A2 synthetase  
RL: USES (Uses)

(inhibitors, phthalazinone, thienopyridazinone, and  
pyridopyridazinone derivs.)

IT 7028-73-1P 137382-05-9P 137382-06-0P 137382-07-1P 137382-08-2P  
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137382-57-1P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, as intermediate for thromboxane A2 synthetase inhibitor  
fused pyridazine derivative)

IT 137381-08-9P 137381-09-0P 137381-10-3P 137381-11-4P 137381-12-5P  
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137382-27-5P	137382-28-6P	137382-29-7P	137382-30-0P	

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as thromboxane A2 synthetase inhibitor)

IT 60-34-4, Methylhydrazine 74-88-4, Methyl iodide, reactions 74-96-4, Ethyl bromide 85-44-9, 1,3-Isobenzofurandione 88-65-3, 2-Bromobenzoic acid 95-46-5, 2-Bromotoluene 100-54-9, 3-Cyanopyridine 100-68-5, Thioanisole 106-93-4, 1,2-Dibromoethane 109-64-8, 1,3-Dibromopropane 110-52-1, 1,4-Dibromobutane 111-24-0, 1,5-Dibromopentane 137-43-9, Cyclopentyl bromide 288-32-4, Imidazole, reactions 288-47-1, Thiazole 288-88-0, (1H)-1,2,4-Triazole 353-83-3, 2,2,2-Trifluoroethyl iodide 626-55-1, 3-Bromopyridine 627-42-9, 2-Methoxyethyl chloride 629-03-8, 1,6-Dibromohexane 630-17-1, 2,2-Dimethylpropyl bromide 872-31-1, 3-Bromothiophene 1766-63-8 2219-66-1, 1,4-Dibromo-2-butyne 3034-53-5, 2-Bromothiazole 3140-93-0, 2,3-Dibromothiophene 4549-32-0, 1,8-Dibromooctane 4595-59-9, 5-Bromopyrimidine 4752-10-7, 1,4-Dichlorophthalazine 5004-45-5, 4-Phenyl-1-(2H)-phthalazinone 5004-48-8, 4-Methyl-1-(2H)-phthalazinone 6164-79-0, Methyl 2-pyrazinecarboxylate 6974-12-5, 1,4-Dibromo-2-butene 7803-57-8, Hydrazine hydrate 18162-48-6, tert-Butyldimethylsilyl chloride 19487-16-2 19686-73-8, 2-Hydroxypropyl bromide 35541-75-4, 1,4-Bis(bromomethyl)cyclohexane 38254-49-8 51334-85-1 51334-86-2 53242-88-9 57353-93-2 75884-68-3 94614-83-2, 1-(2-Bromoethyl)imidazole 97694-84-3 101351-07-9 102990-37-4 102990-38-5 120116-65-6, 6-Chloro-4-phenyl-1-(2H)-phthalazinone 136610-31-6 136610-32-7 137381-15-8 137382-40-2 137382-41-3 137382-42-4 137382-43-5 137382-44-6 137382-45-7 137382-46-8 137382-47-9 137382-48-0 137382-49-1 137382-50-4 137382-51-5 137382-52-6 137382-53-7 137382-54-8 137382-55-9 137382-56-0 137382-58-2 137382-59-3 137382-60-6 137382-61-7 137382-62-8 137382-63-9 137382-64-0 137382-65-1 137401-47-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, in preparation of thromboxane A2 synthetase inhibitor fused pyridazinone derivative)

IT 137382-01-5P

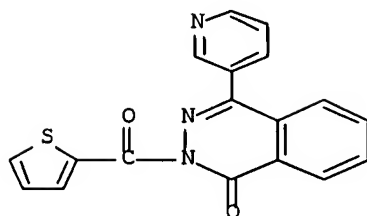
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as thromboxane A2 synthetase inhibitor)

RN 137382-01-5 HCAPLUS

CN 1(2H)-Phthalazinone, 4-(3-pyridinyl)-2-(2-thienylcarbonyl)- (9CI) (CA

INDEX NAME)



L99 ANSWER 28 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1991:81862 HCAPLUS Full-text  
 DOCUMENT NUMBER: 114:81862  
 TITLE: Preparation of heterocyclic oxophthalazinylacetic acids as aldose reductase inhibitors  
 INVENTOR(S): Larson, Eric R.; Mylari, Banavara L.  
 PATENT ASSIGNEE(S): Pfizer Inc., USA  
 SOURCE: U.S., 21 pp. Cont.-in-part of U.S. Ser. No. 136,179.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4939140	A	19900703	US 1988-263577	19881027 <--
CA 1299178	C	19920421	CA 1986-520609	19861016 <--
DD 254001	A5	19880210	DD 1986-296012	19861106 <--
ZA 8608450	A	19880629	ZA 1986-8450	19861106 <--
PRIORITY APPLN. INFO.:			US 1985-796039	B2 19851107 <--
			US 1986-916127	B2 19861007 <--
			US 1987-136179	A2 19871221 <--

OTHER SOURCE(S): MARPAT 114:81862

ED Entered STN: 09 Mar 1991

AB The title compds. I [X = O, S; Z = covalent bond, O, S, NH, CH<sub>2</sub>, or CHR<sub>5</sub>Z = vinylene; R<sub>1</sub> = OH, prodrug group; R<sub>2</sub> = (substituted) (benzo-fused) 5- or 6-membered heterocyclyl, (substituted) imidazolopyridyl, triazolopyridyl, etc.; R<sub>3</sub>, R<sub>4</sub> = H, F, Cl, Br, CF<sub>3</sub>, alkyl, alkoxy, etc.; or R<sub>3</sub>R<sub>4</sub> = alkylenedioxy; R<sub>5</sub> = H, Me, CF<sub>3</sub>] were prepared I are useful as aldose reductase inhibitors (no data). To a mixture of Et 4-oxo-(3H)-phthalazin-1-ylacetate and NaH in DMF was added 2-(bromomethyl)quinoline. The resulting solution was stirred at room temperature for 30 min to give a product, which was saponified to give, after workup, I [X = O, R<sub>1</sub> = OH, R<sub>3</sub> = R<sub>4</sub> = H, CHR<sub>5</sub>ZR<sub>2</sub> = (quinolin-2-yl)methyl].

IC ICM C07D237-32.

ICS C07D519-00; A61K031-50

INCL 514222000

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1, 7

IT 942-06-3P, 4,5-Dichlorophthalic anhydride 1772-01-6P 2941-71-1P  
 4146-24-1P 4760-35-4P 25947-13-1P 40067-66-1P 41014-41-9P  
 50638-17-0P 50710-33-3P 50737-32-1P 50739-39-4P 51802-77-8P

53207-07-1P 55202-19-2P 62248-12-8P 63837-11-6P, 2-Methyl-5-  
bromobenzothiazole 64640-13-7P 74136-78-0P 86793-55-7P  
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benzothiazole 131337-66-1P 131337-67-2P 131337-68-3P  
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 131337-79-6P 131337-80-9P 131337-81-0P, Thieno[2,3-b]pyridine-2-  
 methanol 131337-82-1P 131337-83-2P 131916-64-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation and reaction of, in preparation of aldose reductase inhibitor)

IT 110703-53-2P 110703-54-3P 110703-55-4P 110703-56-5P 110703-57-6P  
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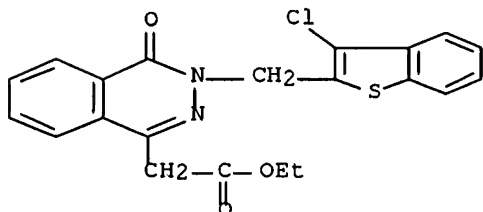
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

IT 131337-82-1P 131337-83-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and reaction of, in preparation of aldose reductase inhibitor)

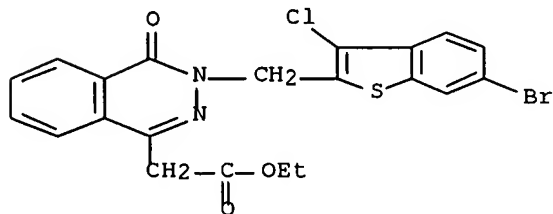
RN 131337-82-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(3-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



RN 131337-83-2 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(6-bromo-3-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



IT 110703-78-1P 110703-92-9P 124168-18-9P

124168-19-0P 124168-20-3P 124168-21-4P

124168-23-6P 124168-24-7P 131337-35-4P

131337-36-5P 131337-37-6P 131337-38-7P

131337-39-8P 131337-40-1P 131337-48-9P

131337-49-0P 131337-50-3P 131337-51-4P

131337-52-5P 131337-53-6P

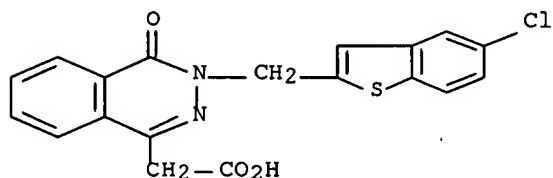
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

10/518,503

(preparation of, as aldose reductase inhibitor)

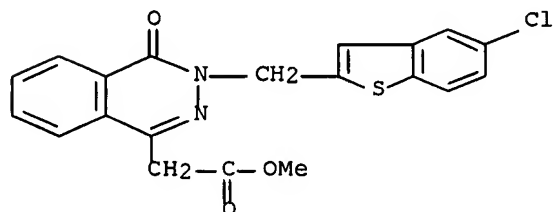
RN 110703-78-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



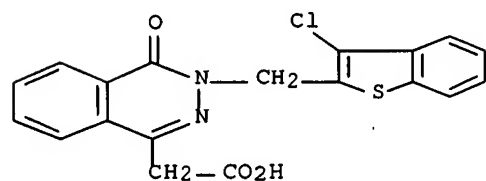
RN 110703-92-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



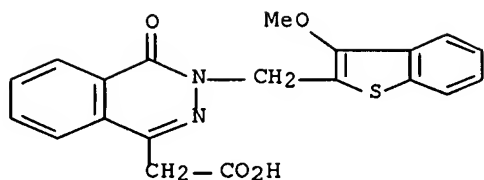
RN 124168-18-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(3-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



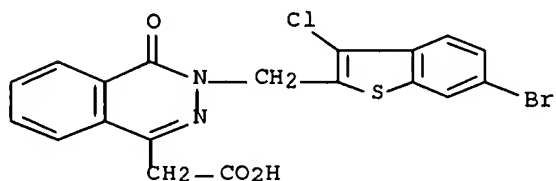
RN 124168-19-0 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(3-methoxybenzo[b]thien-2-yl)methyl]-4-oxo- (9CI) (CA INDEX NAME)



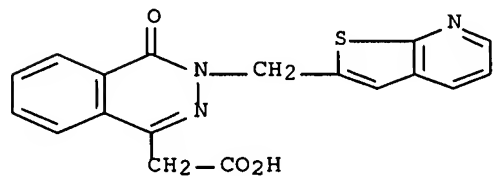
RN 124168-20-3 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(6-bromo-3-chlorobenzo[b]thien-2-yl)methyl]-  
3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



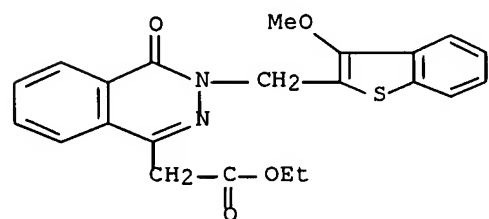
RN 124168-21-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-ylmethyl)- (9CI) (CA INDEX NAME)



RN 124168-23-6 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(3-methoxybenzo[b]thien-2-yl)methyl]-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

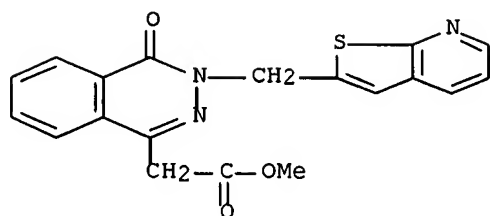


RN 124168-24-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-

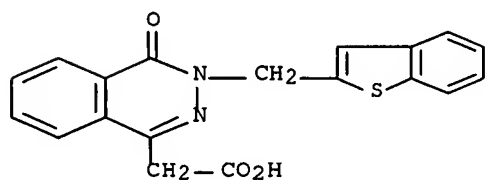
10/518,503

ylmethyl)-, methyl ester (9CI) (CA INDEX NAME)



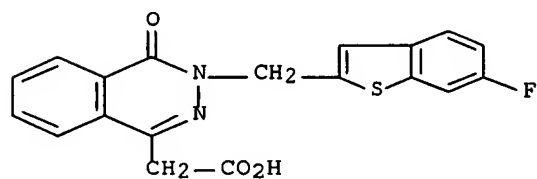
RN 131337-35-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3-(benzo[b]thien-2-ylmethyl)-3,4-dihydro-4-oxo-  
(9CI) (CA INDEX NAME)



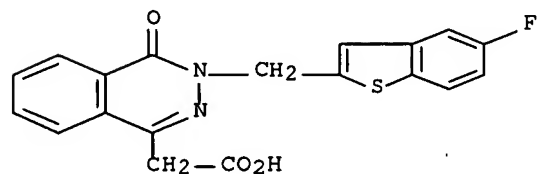
RN 131337-36-5 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(6-fluorobenzo[b]thien-2-yl)methyl]-3,4-  
dihydro-4-oxo- (9CI) (CA INDEX NAME)



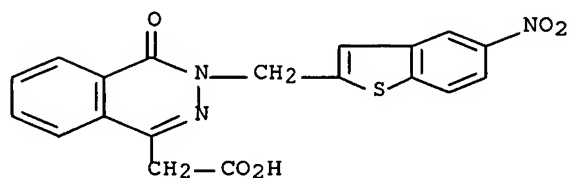
RN 131337-37-6 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-fluorobenzo[b]thien-2-yl)methyl]-3,4-  
dihydro-4-oxo- (9CI) (CA INDEX NAME)



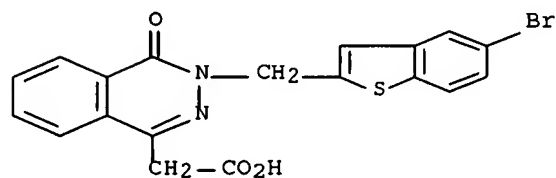
RN 131337-38-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(5-nitrobenzo[b]thien-2-yl)methyl]-4-oxo- (9CI) (CA INDEX NAME)



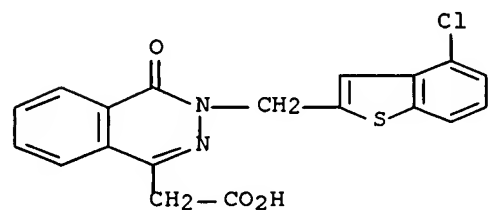
RN 131337-39-8 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-bromobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



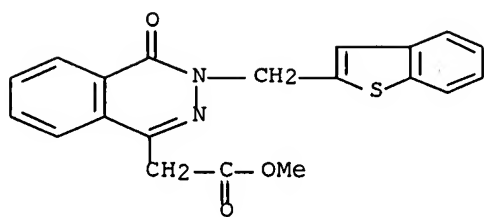
RN 131337-40-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(4-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



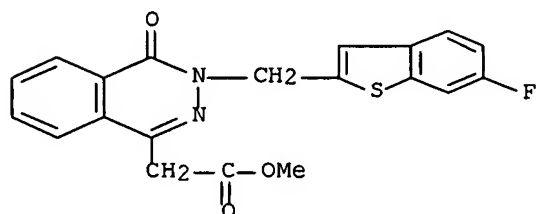
RN 131337-48-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-(benzo[b]thien-2-ylmethyl)-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



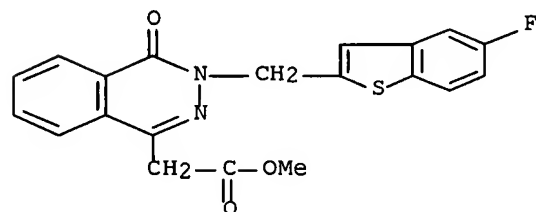
RN 131337-49-0 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(6-fluorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



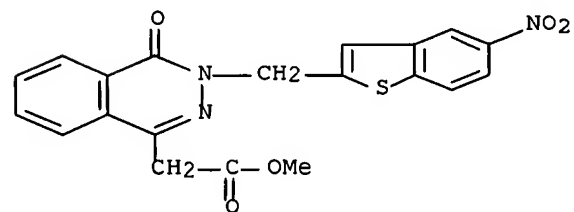
RN 131337-50-3 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-fluorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



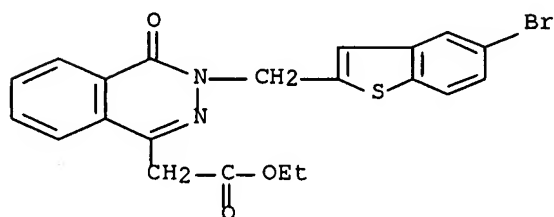
RN 131337-51-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(5-nitrobenzo[b]thien-2-yl)methyl]-4-oxo-, methyl ester (9CI) (CA INDEX NAME)



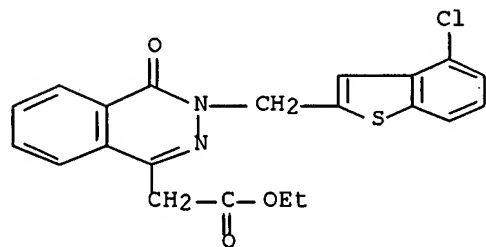
RN 131337-52-5 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-bromobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



RN 131337-53-6 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(4-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



L99 ANSWER 29 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:164264 HCAPLUS Full-text

DOCUMENT NUMBER: 114:164264

TITLE: Preparation of pyridopyridazinylacetates as  
aldose reductase inhibitors

INVENTOR(S): Mylari, Banavara Lakshmana; Zembrowski, William James

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 401981	A1	19901212	EP 1990-305015	19900510 <--
EP 401981	B1	19950426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4996204	A	19910226	US 1989-350417	19890511 <--
CA 2016326	A1	19901111	CA 1990-2016326	19900509 <--
CA 2016326	C	19950530		
NO 9002070	A	19901112	NO 1990-2070	19900510 <--
NO 173938	B	19931115		

NO 173938	C	19940223		
AU 9054905	A	19901115	AU 1990-54905	19900510 <--
AU 611610	B2	19910613		
HU 54683	A2	19910328	HU 1990-2996	19900510 <--
HU 206714	B	19921228		
ZA 9003564	A	19920826	ZA 1990-3564	19900510 <--
FI 93013	B	19941031	FI 1990-2335	19900510 <--
FI 93013	C	19950210		
AT 121743	T	19950515	AT 1990-305015	19900510 <--
ES 2071016	T3	19950616	ES 1990-305015	19900510 <--
JP 03005481	A	19910111	JP 1990-122832	19900511 <--
JP 06031235	B	19940427		
PRIORITY APPLN. INFO.:			US 1989-350417	A 19890511 <--
OTHER SOURCE(S):			MARPAT 114:164264	
ED	Entered STN: 03 May 1991			
AB	The title compds. [I and II; R = H, Me; W = bond, CH <sub>2</sub> ; CRHW = vinyl; X = H, F, Cl, Br, CF <sub>3</sub> , alkyl, alkoxy, alkylthio; Y = O, S; Z = (substituted) Ph, <u>thiazolophenyl</u> , <u>benzothioophenyl</u> , <u>benzoxazolyl</u> , <u>benzothiazolyl</u> , <u>oxazolopyridinyl</u> , <u>imidazopyridinyl</u> , <u>indolyl</u> , <u>triazolopyridinyl</u> , etc.], and salts and esters thereof, were prepared Thus, tert-Bu 5-oxo-6H-pyrido[2,3-d]pyridazine-8-ylacetate (preparation starting from 2,3-pyridinedicarboxylic anhydride and Me <sub>3</sub> OP <sub>2</sub> CCH <sub>2</sub> PPh <sub>3</sub> given), KOCMe <sub>3</sub> , and 2-chloromethyl-5- <u>trifluoromethylbenzothiazole</u> were stirred overnight to give 69% coupling product, which was stirred with aqueous H <sub>2</sub> SO <sub>4</sub> to give 53% 6-(5- <u>trifluoromethylbenzothiazole</u> -2-ylmethyl)-5-oxo-6H-pyrido[2,3-d]pyridazin-8-ylacetic acid. The latter at 10 <sup>-7</sup> M gave 74% inhibition of aldose reductase in the procedure of S. Hayman.			
IC	ICM C07D471-04 ICS A61K031-50			
ICI	C07D471-04, C07D237-00, C07D221-00			
CC	28-15 (Heterocyclic Compounds (More Than One Hetero Atom)) Section cross-reference(s): 1			
ST	<u>pyridopyridazinylacetate</u> prepn aldose reductase inhibitor; <u>pyridazinylacetate</u> pyrido aldose reductase inhibitor; cataract treatment <u>pyridopyridazinylacetate</u> ; retinopathy treatment <u>pyridopyridazinylacetate</u> ; nephropathy treatment <u>pyridopyridazinylacetate</u> ; neuropathy treatment <u>pyridopyridazinylacetate</u>			
IT	Diabetes mellitus (complications from, <u>pyridopyridazinylacetates</u> for)			
IT	Cataract (treatment of, <u>pyridopyridazinylacetates</u> )			
IT	Eye, disease or disorder (retinopathy, treatment of, <u>pyridopyridazinylacetates</u> )			
IT	76283-09-5, 4-Bromo-2-fluorobenzyl bromide 110704-50-2 110704-60-4, 2-Chloromethyl-5- <u>fluorobenzothiazole</u> 126764-53-2, 2-Chloromethyl-5,7- <u>difluorobenzothiazole</u> 131337-71-8, 4-Chloro-2- <u>chloromethylbenzothiophene</u> 133122-57-3, 5-Bromo-2-bromomethylbenzoxazole 133144-89-5 RL: RCT (Reactant); RACT (Reactant or reagent) (condensation of, with <u>pyridopyridazinylacetate</u> , in preparation of aldose reductase inhibitor)			
IT	302-01-2, Hydrazine, reactions RL: RCT (Reactant); RACT (Reactant or reagent) (cyclocondensation of, with (oxopyridofuranylidene)acetate, in preparation of <u>pyridopyridazinylacetate</u> )			
IT	9028-31-3, Aldose reductase RL: USES (Uses) (inhibitors, <u>pyridopyridazinylacetates</u> )			
IT	131106-55-3P 131666-80-3P 133122-41-5P 133122-42-6P 133122-43-7P			

133122-44-8P 133122-45-9P 133122-46-0P 133122-47-1P  
 133122-48-2P 133122-49-3P 133122-50-6P 133122-51-7P  
 133122-52-8P 133122-53-9P 133122-54-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

IT 133122-55-1P 133122-56-2P

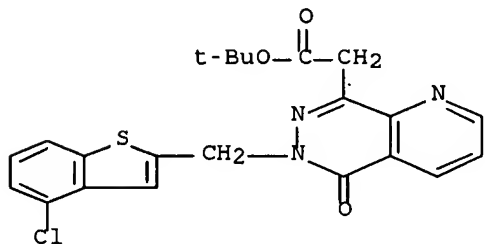
RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as intermediate for pyridopyridazinylacetate  
 aldose reductase inhibitor)

IT 133122-44-8P 133122-52-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

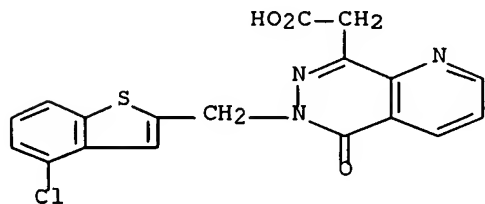
RN 133122-44-8 HCAPLUS

CN Pyrido[2,3-d]pyridazine-8-acetic acid, 6-[(4-chlorobenzo[b]thien-2-yl)methyl]-5,6-dihydro-5-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 133122-52-8 HCAPLUS

CN Pyrido[2,3-d]pyridazine-8-acetic acid, 6-[(4-chlorobenzo[b]thien-2-yl)methyl]-5,6-dihydro-5-oxo- (9CI) (CA INDEX NAME)



L99 ANSWER 30 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1989:553824 HCAPLUS Full-text

DOCUMENT NUMBER: 111:153824

TITLE: 5-(4-Oxo-1-phthalazinyl)-2,4-dioxothiazolidine

derivatives as aldose reductase inhibitors

INVENTOR(S): Niigata, Kunihiro; Okada, Minoru; Yoneda, Takashi

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 13 pp.

DOCUMENT TYPE: CODEN: JKXXAF  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: 1 Japanese  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01019077	A	19890123	JP 1987-175264	19870713 <--
PRIORITY APPLN. INFO.:			JP 1987-175264	19870713 <--

OTHER SOURCE(S): MARPAT 111:153824

ED Entered STN: 28 Oct 1989

AB Title compds. I [X = H, halo; n = 1,2; R = H, alkyl substituted phenyl-, (halo-substituted)imidazolyl- or thienyl-, naphthyl-, or 2-alkyl-5-halothiazol-4-ylalkyl], useful for treatment of diabetic complications such as diseases caused by aldose reductase (no data), are prepared Treatment of a phthalazine II (R1 = CH2CO2Et) (generated in situ from its HBr salt) in CHCl3 with Br in the presence of (PhCO)2O2 under a 300W lamp gave II (R1 = CHBrCO2Et), which in EtOH was refluxed with (H2N)2CS to afford II (R1 = 2,4-dioxothiazolidin-5-yl).

IC ICM C07D417-04  
 ICS A61K031-50; C07D417-14

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1

ST oxophthalazinyldioxothiazolidine prepn aldose reductase inhibitor; phthalazine dioxothiazolidinyl aldose reductase inhibitor; thiazolidine phthalazinyl aldose reductase inhibitor

IT Diabetes insipidus  
 Diabetes mellitus  
 (complications from, treatment of, by oxophthalazinyldioxothiazolidine derivs.)

IT 9028-31-3, Aldose reductase  
 RL: USES (Uses)  
 (inhibitors, oxophthalazinyldioxothiazolidine derivs. as)

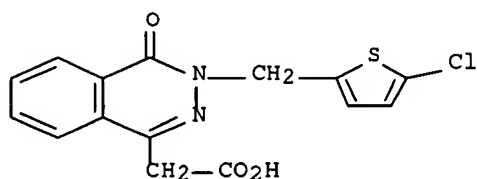
IT 72702-92-2P 122812-84-4P 122812-85-5P 122812-86-6P 122812-87-7P  
 122812-88-8P 122812-89-9P 122812-90-2P 122812-91-3P  
122812-92-4P 122812-93-5P 122812-94-6P 122812-95-7P  
 122812-96-8P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and reaction of, in preparation of oxophthalazinyldioxothiazolidine aldose reductase inhibitors)

IT 122812-67-3P 122812-68-4P 122812-69-5P 122812-70-8P 122812-71-9P  
 122812-72-0P 122812-73-1P 122812-74-2P 122812-75-3P 122812-76-4P  
 122812-77-5P 122812-78-6P 122812-79-7P 122812-80-0P  
 122812-81-1P 122812-82-2P 122812-83-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

IT 23784-96-5, 2-Chloro-5-chloromethylthiophene  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (N-alkylation by, of phthalazine derivative)

IT 122812-92-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and reaction of, in preparation of oxophthalazinyldioxothiazolidine aldose reductase inhibitors)

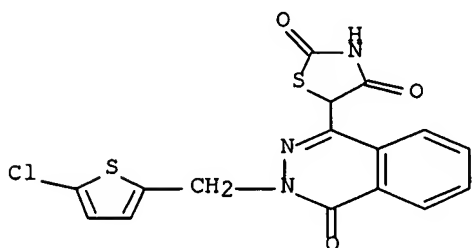
RN 122812-92-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chloro-2-thienyl)methyl]-3,4-dihydro-4-oxo-  
(9CI) (CA INDEX NAME)IT **122812-78-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of, as aldose reductase inhibitor)

RN 122812-78-6 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[3-[(5-chloro-2-thienyl)methyl]-3,4-dihydro-4-oxo-1-phthalazinyl]- (9CI) (CA INDEX NAME)



L99 ANSWER 31 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:7498 HCAPLUS Full-text

DOCUMENT NUMBER: 112:7498

TITLE: Oxophthalazineacetates as aldose reductase inhibitors

INVENTOR(S): Larson, Eric Robert; Mylari, Banavara Lakshmana

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: Eur. Pat. Appl., 21 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 322153	A2	19890628	EP 1988-311857	19881215 <--
EP 322153	A3	19900816		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1299181	C	19920421	CA 1988-586121	19881216 <--
IL 88729	A	19960723	IL 1988-88729	19881219 <--
FI 8805886	A	19890622	FI 1988-5886	19881220 <--

10/518,503

HU 56552	A2	19910930	HU 1988-6506	19881220 <--
HU 207086	B	19930301		
AU 8827337	A	19890622	AU 1988-27337	19881221 <--
AU 609559	B2	19910502		
DK 8807123	A	19890731	DK 1988-7123	19881221 <--
JP 01211585	A	19890824	JP 1988-323225	19881221 <--
JP 06092402	B	19941116		
CN 1035116	A	19890830	CN 1988-109263	19881221 <--
DD 276686	A5	19900307	DD 1988-323606	19881221 <--
ZA 8809519	A	19900829	ZA 1988-9519	19881221 <--

## PRIORITY APPLN. INFO.:

US 1987-136179 A 19871221 &lt;--

ED Entered STN: 06 Jan 1990

AB Title compds. I (X = O, S; Z = bond, O, S, NH, CH<sub>2</sub>; CHR1Z = CH:CH; R1 = OH, groups for prodrug; R2 = heterocyclyl, e.g., imidazolopyridyl, thienopyridyl, and pyrrolyl; R3,R4 = H, F, Cl, Br, CF<sub>3</sub>, alkyl, alkoxy, alkylsulfonyl, etc.; R3R4 = C1-4 alkylenedioxy; R5 = H, Me, CF<sub>3</sub>), useful as aldose reductase inhibitors (no data), are prepared Treatment of Et 4-oxo-3H-phthalazin-1-ylacetate in DMF with tert-BuOK and then a benzothiazole QCl (R = Me) (preparation given) gave I [R1 = EtO; R3 = R4 = H; X = O; CHR5ZR2 = Q (R = Me)]. Saponification of the latter with aqueous KOH in THF/EtOH, followed by demethylation with HBr gave I (R1 = OH; R = R3 = R4 = H; X = O; CHR5ZR2 = Q).

IC ICM C07D417-06

ICS C07D409-06; C07D471-04; C07D411-06; C07D407-06; C07D403-06; A61K031-50

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT 110704-61-5P 122665-79-6P 124168-10-1P 124168-11-2P 124168-12-3P  
 124168-13-4P 124168-14-5P 124168-15-6P 124168-16-7P 124168-17-8P

124168-18-9P 124168-19-0P 124168-20-3P124168-21-4P 124168-22-5P 124168-23-6P124168-24-7P 124168-25-8P 124168-26-9P 124168-27-0P

124168-28-1P 124168-29-2P 124168-30-5P 124168-31-6P 124168-32-7P

124168-33-8P 124168-34-9P 124168-35-0P 124168-36-1P 124168-37-2P

124168-38-3P 124168-39-4P 124168-40-7P 124168-41-8P 124168-42-9P

124168-43-0P

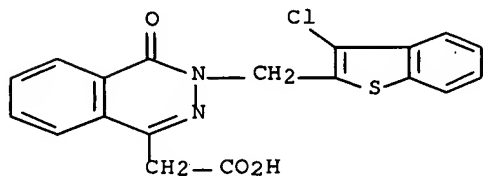
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

IT 124168-18-9P 124168-19-0P 124168-20-3P124168-21-4P 124168-23-6P 124168-24-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of, as aldose reductase inhibitor)

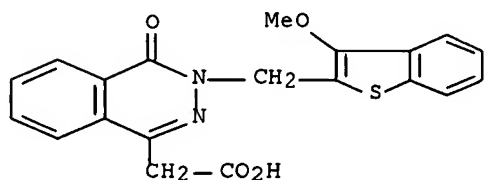
RN 124168-18-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(3-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



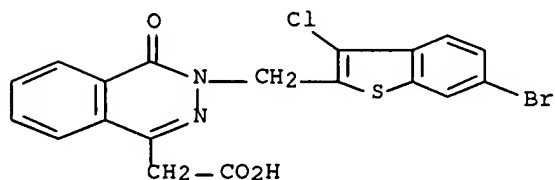
RN 124168-19-0 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(3-methoxybenzo[b]thien-2-yl)methyl]-4-oxo- (9CI) (CA INDEX NAME)



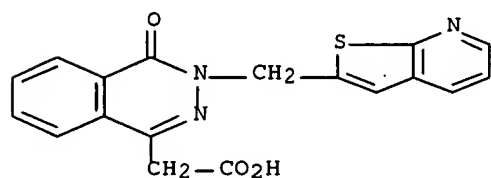
RN 124168-20-3 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(6-bromo-3-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



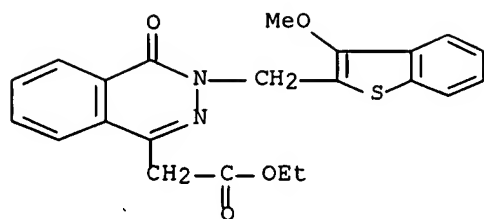
RN 124168-21-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-ylmethyl)- (9CI) (CA INDEX NAME)



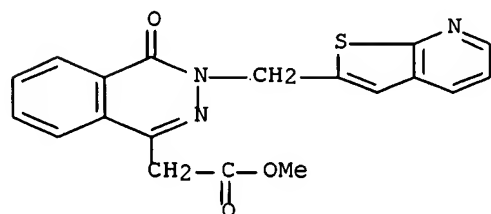
RN 124168-23-6 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-3-[(3-methoxybenzo[b]thien-2-yl)methyl]-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



RN 124168-24-7 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-(thieno[2,3-b]pyridin-2-ylmethyl)-, methyl ester (9CI) (CA INDEX NAME)



L99 ANSWER 32 OF 69 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1987:576055 HCAPLUS Full-text

DOCUMENT NUMBER: 107:176055

TITLE: Preparation of heterocyclic oxophthalazinyl acetic acids derivatives

INVENTOR(S): Mylari, Banavara Lakshmana; Larson, Eric Robert; Zembrowski, William James

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: Eur. Pat. Appl., 41 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 222576	A2	19870520	EP 1986-308545	19861103 <--
EP 222576	A3	19880323		
EP 222576	B1	19920318		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4723010	A	19880202	US 1985-796359	19851107 <--
CA 1299178	C	19920421	CA 1986-520609	19861016 <--
AT 73801	T	19920415	AT 1986-308545	19861103 <--
IL 80475	A	19930131	IL 1986-80475	19861103 <--
ES 2032749	T3	19930301	ES 1986-308545	19861103 <--
CA 1293726	C	19911231	CA 1986-522156	19861104 <--
DK 8605298	A	19870508	DK 1986-5298	19861106 <--
DK 172010	B1	19970915		
FI 8604512	A	19870508	FI 1986-4512	19861106 <--
FI 87355	B	19920915		

FI 87355	C	19921228		
AU 8664858	A	19870611	AU 1986-64858	19861106 <--
AU 574589	B2	19880707		
CN 86108308	A	19870715	CN 1986-108308	19861106 <--
CN 1009831	B	19901003		
DD 254001	A5	19880210	DD 1986-296012	19861106 <--
ZA 8608450	A	19880629	ZA 1986-8450	19861106 <--
HU 46318	A2	19881028	HU 1986-4621	19861106 <--
HU 206338	B	19921028		
SU 1551246	A3	19900315	SU 1986-4028554	19861106 <--
NO 168303	B	19911028	NO 1986-4425	19861106 <--
NO 168303	C	19920205		
JP 62114988	A	19870526	JP 1986-265436	19861107 <--
JP 04001747	B	19920114		
PL 151024	B1	19900731	PL 1986-262266	19861107 <--
US 4748280	A	19880531	US 1987-79869	19870731 <--
CA 1290768	C2	19911015	CA 1990-615750	19900528 <--
PRIORITY APPLN. INFO.:			US 1985-796039	A 19851107 <--
			US 1985-796359	A 19851107 <--
			EP 1986-308545	A 19861103 <--
			CA 1986-522156	A 19861104 <--

OTHER SOURCE(S): CASREACT 107:176055; MARPAT 107:176055

ED Entered STN: 14 Nov 1987

AB The title compds. [I; R1 = OH, 'prodrug' group; R2 = (substituted) (benzo-fused) N-containing 5- or 6-membered heterocyclyl; R3, R4 = H, F, Cl, Br, CF3, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, NO2; R3R4 = alkanedioxy; R5 = H, Me; X = O, S; Z = bond, O, S, NH, CH2] were prepared as aldose reductase inhibitors for treatment of diabetes-associated disorders (no data). Et 4-oxo-3H-phthalazine-1-ylacetate 11.5 g, NaH, and 5-bromo-2-(bromomethyl)benzothiazole 16.8 g were stirred in DMF for 1 h at room temperature to give 15.6 g I (R1 = OEt, R2 = 5- bromobenzothiazol-2-yl, R3 = R4 = R5 = H, X = Z = O) which (15.0 g) was saponified with KOH in dioxane to give 7.65 g I (R1 = OH).

IC ICM C07D417-06

ICS C07D413-14; C07D413-06; C07D403-06; C07D498-04; C07D417-12; C07D409-06; C07D513-04; A61K031-50

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

ST benzothiazolymethylphthalazinylacetate prepn aldose reductase inhibitor; cataract treatment benzothiazolymethylphthalazinylacetate; retinopathy treatment benzothiazolymethylphthalazinylacetate\*  
\*\* ; neuropathy treatment \*\*\*benzothiazolymethylphthalazineacetate  
 ; phthalazinylacetate heterocyclyl diabetes treatment;  
 oxadiazolymethylphthalazinylacetate prepn aldose reductase inhibitor

IT 25947-14-2

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (alkylation of, by (bromomethyl)benzothiazole)

IT 25947-13-1

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (alkylation of, by (bromomethyl)benzothiazole, in preparation of  
 aldose reductase inhibitors)

IT 137-07-5, 2-Aminothiophenol 4274-38-8 16867-03-1,  
 2-Amino-3-hydroxypyridine 38240-21-0, 3-Amino-2-mercaptopyridine  
 79811-34-0D, tin complex

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (cyclocondensation of, with chlorotriethoxyethane)

IT 110704-51-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation and cyclization of, benzothiazole derivative by)

IT	110703-53-2P	110703-54-3P	110703-55-4P	110703-56-5P	110703-57-6P
	110703-58-7P	110703-59-8P	110703-60-1P	110703-61-2P	110703-62-3P
	110703-63-4P	110703-64-5P	110703-65-6P	110703-66-7P	110703-67-8P
	110703-68-9P	110703-69-0P	110703-70-3P	110703-71-4P	110703-72-5P
	110703-73-6P	110703-74-7P	<u>110703-75-8P</u>	<u>110703-76-9P</u>	
	110703-77-0P	<u>110703-78-1P</u>	110703-79-2P	110703-80-5P	
	110703-81-6P	110703-82-7P	110703-83-8P	110703-84-9P	110703-85-0P
	110703-86-1P	110703-87-2P	110703-88-3P	<u>110703-89-4P</u>	
	<u>110703-90-7P</u>	110703-91-8P	<u>110703-92-9P</u>	110703-93-0P	
	110703-94-1P	110703-95-2P	110703-96-3P	110703-97-4P	110703-98-5P
	110703-99-6P	110704-00-2P	110704-01-3P	110704-02-4P	110704-53-5P
	110704-61-5P	110721-48-7P	110721-49-8P	110721-50-1P	110721-51-2P
	110721-52-3P	110721-53-4P	110721-54-5P	110721-55-6P	110721-56-7P
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	110721-62-5P	110721-63-6P	110721-64-7P	110721-65-8P	110721-66-9P
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	110721-87-4P	110721-88-5P	110721-89-6P	110721-90-9P	110721-91-0P
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	110722-34-4P	110722-35-5P	110722-36-6P	110722-37-7P	110722-38-8P
	110722-39-9P	110722-40-2P	110722-41-3P	110722-42-4P	110722-43-5P
	110722-44-6P	110722-45-7P	110722-46-8P	110749-07-0P	110749-08-1P
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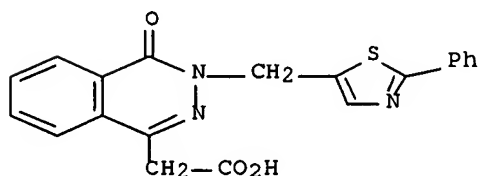
RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as aldose reductase inhibitor for treatment of  
 diabetes-associated diseases)

IT 110703-75-8P 110703-76-9P 110703-78-1P  
110703-89-4P 110703-90-7P 110703-92-9P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as aldose reductase inhibitor for treatment of  
 diabetes-associated diseases)

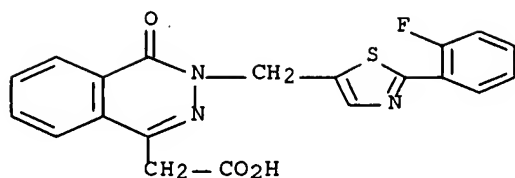
RN 110703-75-8 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[(2-phenyl-5-thiazolyl)methyl]- (9CI) (CA INDEX NAME)



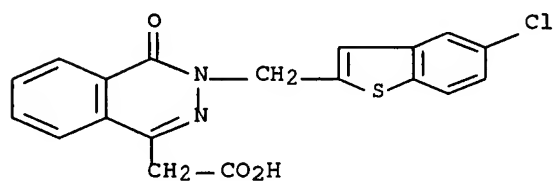
RN 110703-76-9 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[[2-(2-fluorophenyl)-5-thiazolyl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



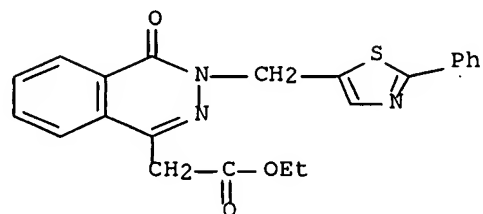
RN 110703-78-1 HCAPLUS

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



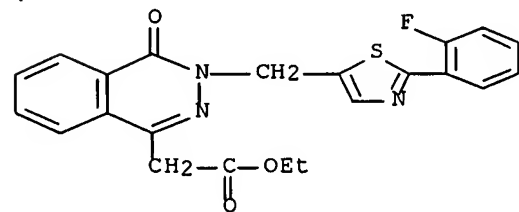
RN 110703-89-4 HCAPLUS

CN 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[(2-phenyl-5-thiazolyl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 110703-90-7 HCAPLUS

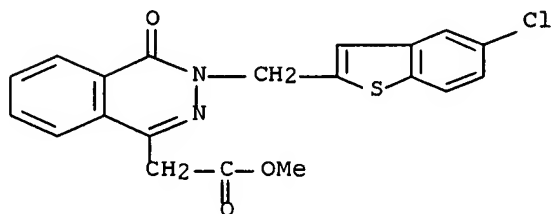
CN 1-Phthalazineacetic acid, 3-[[2-(2-fluorophenyl)-5-thiazolyl]methyl]-3,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



RN 110703-92-9 HCAPLUS

10/518,503

CN 1-Phthalazineacetic acid, 3-[(5-chlorobenzo[b]thien-2-yl)methyl]-3,4-dihydro-4-oxo-, methyl ester (9CI) (CA INDEX NAME)

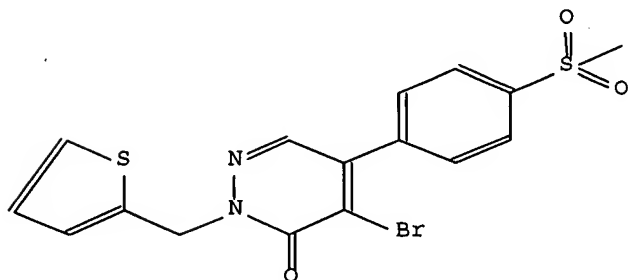


=> d 150 ide

YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L50 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2006 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9344517
Chemical Name (CN):	4-bromo-5-(4-methanesulfonyl-phenyl)-2-thiophen-2-ylmethyl-2H-pyridazin-3-one
Autonom Name (AUN):	4-bromo-5-(4-methanesulfonyl-phenyl)-2-thiophen-2-ylmethyl-2H-pyridazin-3-one
Molec. Formula (MF):	C16 H13 Br N2 O3 S2
Molecular Weight (MW):	425.31
Lawson Number (LN):	29066, 20730, 292
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	7888607
Tautomer ID (TAUTID):	8768875
Entry Date (DED):	2003/07/25
Update Date (DUPD):	2003/07/25



Field Availability:

Code	Name	Occurrence
=====		

BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

=> d 150 rx

YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L50 ANSWER 1 OF 1 BEILSTEIN COPYRIGHT 2006 BEILSTEIN MDL on STN

Reaction:

RX

Reaction ID (.ID):	9250928
Reactant BRN (.RBRN):	9332509
Reactant (.RCT):	4-bromo-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one, 2-thienylmethyl halide
Product BRN (.PBRN):	9344517
Product (.PRO):	4-bromo-5-(4-methanesulfonyl-phenyl)-2-thiophen-2-ylmethyl-2H-pyridazin-3-one
No. of React. Details (.NVAR):	1

Reaction Details:

RX

Reaction RID (.RID):	9250928.1
Reaction Classification (.CL):	Preparation
Reagent (.RGT):	base
Reference(s):	
1. Li, Chun Sing; Brideau, Christine; Chan, Chi Chung; Savoie, Chantal; Claveau, David; Charleson, Stella; Gordon, Robert; Greig, Gillian; Gauthier, Jacques Yves; Lau, Cheuk K.; Riendeau, Denis; et al., Bioorg.Med.Chem.Lett., CODEN: BMCLE8, 13(4), <2003>, 597 - 600; BABS-6388164	

Reaction:

RX

Reaction ID (.ID):	9250533
Reactant BRN (.RBRN):	9344517, 2829653
Reactant (.RCT):	4-bromo-5-(4-methanesulfonyl-phenyl)-2-thiophen-2-ylmethyl-2H-pyridazin-3-one, (4-fluoro-phenyl)-dihydroxy-borane

10/518,503

Product BRN (.PBRN): 9353562  
Product (.PRO): 4-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2-thiophen-2-ylmethyl-2H-pyridazin-3-one  
No. of React. Details (.NVAR): 1

Reaction Details:

RX

Reaction RID (.RID): 9250533.1  
Reaction Classification (.CL): Preparation  
Catalyst (.CAT): Pd(0)  
Reaction Type (.TYP): Suzuki coupling  
Reference(s):

1. Li, Chun Sing; Brideau, Christine; Chan, Chi Chung; Savoie, Chantal; Claveau, David; Charleson, Stella; Gordon, Robert; Greig, Gillian; Gauthier, Jacques Yves; Lau, Cheuk K.; Riendeau, Denis; et al., Bioorg.Med.Chem.Lett., CODEN: BMCLE8, 13(4), <2003>, 597 - 600; BABS-6388164

=> d ibib ab hitstr 33-34

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE, DRUGU, MARPAT' - CONTINUE? (Y)/N:y

L99 ANSWER 33 OF 69 USPATFULL on STN

ACCESSION NUMBER: 2005:255662 USPATFULL Full-text  
TITLE: Thiazole derivatives as phosphodiesterase iv inhibitors  
INVENTOR(S): Eggenweiler, Hans-Michael, Darmstadt, GERMANY, FEDERAL REPUBLIC OF  
Wolf, Michael, Darmstadt, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005222160	A1	20051006
APPLICATION INFO.:	US 2003-518503	A1	20030428 (10)
	WO 2003-EP4434		20030428
			20041220 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	DE 2002-10227269	20020619
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201, US	
NUMBER OF CLAIMS:	29	
EXEMPLARY CLAIM:	1	
LINE COUNT:	3103	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Thiazole derivatives of the formula I ##STR1## in which R.sup.1, R.sup.2, R.sup.3, V, W, X and B are as defined in claim 1, act as phosphodiesterase IV inhibitors and can be employed for the treatment of osteoporosis, tumours, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases and AIDS.

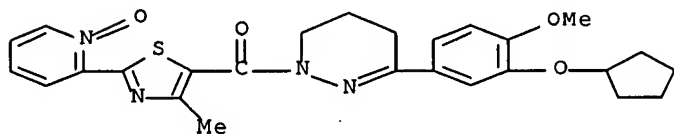
IT 640743-35-7P 640743-36-8P 640743-37-9P  
640743-38-0P, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-

pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone  
**640743-39-1P**, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone  
**640743-40-4P**, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone  
**640743-41-5P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone  
**640743-42-6P**, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone  
**640743-43-7P**, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone  
**640743-44-8P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone  
**640743-45-9P**, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone  
**640743-46-0P**, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone  
**640743-47-1P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone  
**640743-48-2P**, 1-[3-(3-Isopropoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone  
**640743-49-3P**, 1-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone  
**640743-50-6P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-(4-methyl-2-phenylthiazol-5-yl)methanone  
**640743-51-7P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-methoxyphenyl)thiazol-5-yl]methanone  
**640743-52-8P**, 1-[3-(3-Ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-1-[4-methyl-2-(4-aminophenyl)thiazol-5-yl]methanone  
**640743-53-9P 640743-54-0P**

(drug candidate; preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

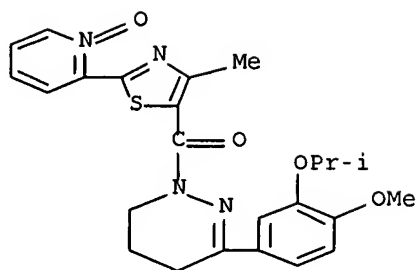
RN 640743-35-7 USPTAFULL

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



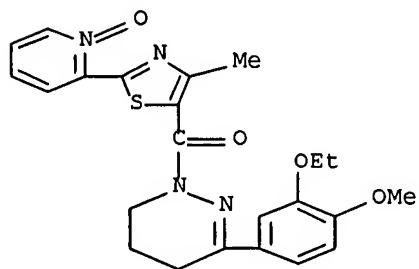
RN 640743-36-8 USPTAFULL

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



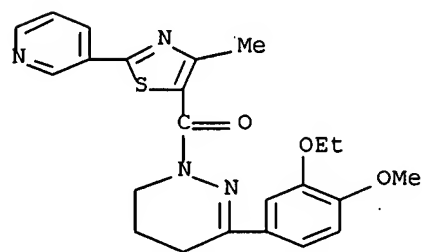
RN 640743-37-9 USPTAFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(1-oxido-2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



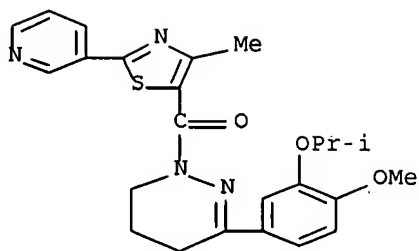
RN 640743-38-0 USPTAFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



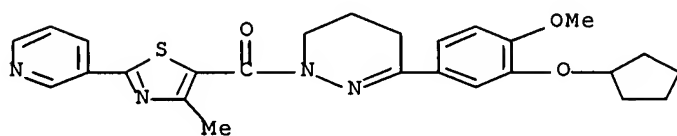
RN 640743-39-1 USPTAFULL

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



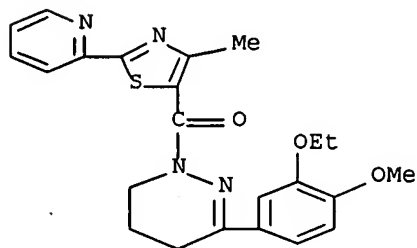
RN 640743-40-4 USPATFULL

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(3-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



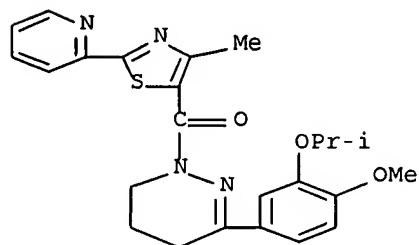
RN 640743-41-5 USPATFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

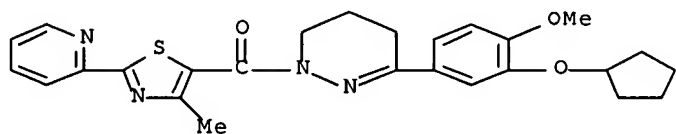


RN 640743-42-6 USPATFULL

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

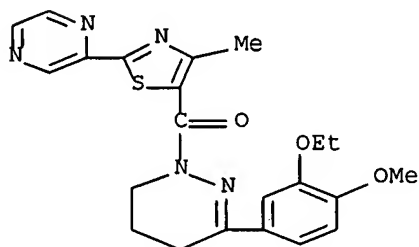


RN 640743-43-7 USPATFULL

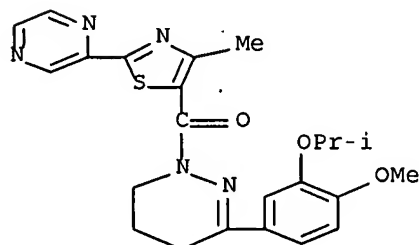
CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-  
[[4-methyl-2-(2-pyridinyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

RN 640743-44-8 USPATFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[(4-methyl-2-pyrazinyl-5-thiazolyl)carbonyl]- (9CI) (CA INDEX NAME)

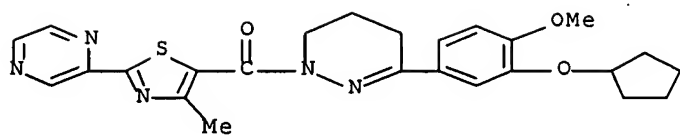


RN 640743-45-9 USPATFULL

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-  
[(4-methyl-2-pyrazinyl-5-thiazolyl)carbonyl]- (9CI) (CA INDEX NAME)

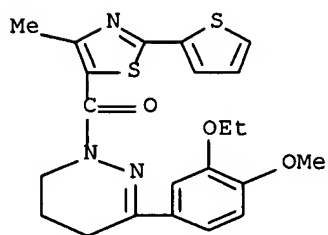
RN 640743-46-0 USPATFULL

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-  
[(4-methyl-2-pyrazinyl-5-thiazolyl)carbonyl]- (9CI) (CA INDEX NAME)



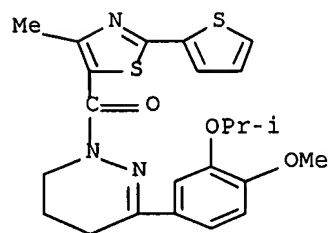
RN 640743-47-1 USPATFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



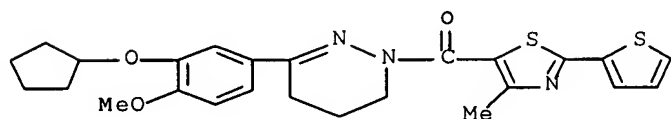
RN 640743-48-2 USPATFULL

CN Pyridazine, 1,4,5,6-tetrahydro-3-[4-methoxy-3-(1-methylethoxy)phenyl]-1-[[4-methyl-2-(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



RN 640743-49-3 USPATFULL

CN Pyridazine, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,4,5,6-tetrahydro-1-[[4-methyl-2-(2-thienyl)-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)

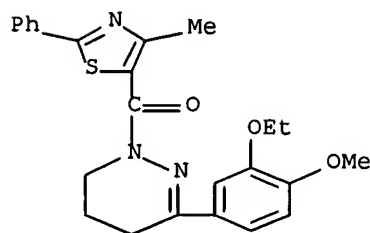


RN 640743-50-6 USPATFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[4-methyl-2-

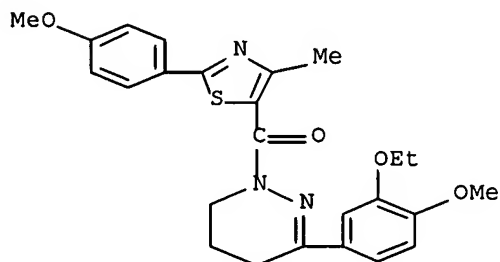
10/518,503

phenyl-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



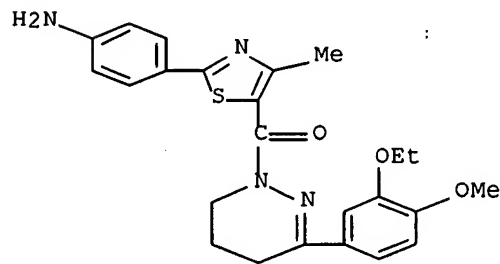
RN 640743-51-7 USPATFULL

CN Pyridazine, 3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-1-[[2-(4-methoxyphenyl)-4-methyl-5-thiazolyl]carbonyl]- (9CI) (CA INDEX NAME)



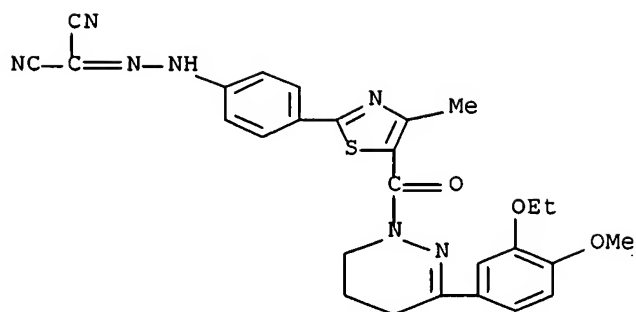
RN 640743-52-8 USPATFULL

CN Pyridazine, 1-[[2-(4-aminophenyl)-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



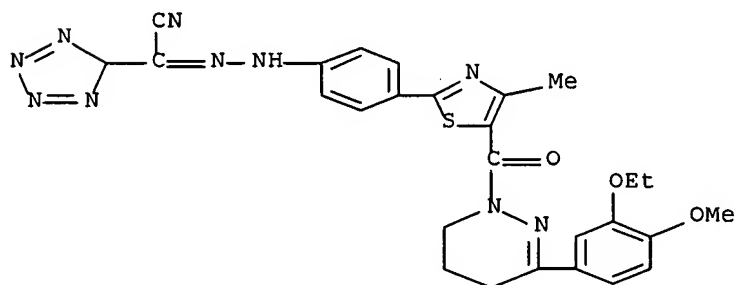
RN 640743-53-9 USPATFULL

CN Pyridazine, 1-[[2-[4-[(dicyanomethylene)hydrazino]phenyl]-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



RN 640743-54-0 USPATFULL

CN Pyridazine, 1-[[2-[4-[(cyano-5H-tetrazol-5-ylmethylene)hydrazino]phenyl]-4-methyl-5-thiazolyl]carbonyl]-3-(3-ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)

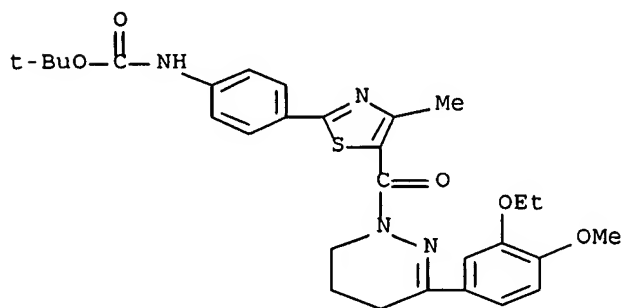


IT 640743-64-2

(preparation of thiazoles as phosphodiesterase IV inhibitors for the treatment of osteoporosis, tumors and cachexia)

RN 640743-64-2 USPATFULL

CN Carbamic acid, [4-[5-[[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-1(4H)-pyridazinyl]carbonyl]-4-methyl-2-thiazolyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



ACCESSION NUMBER: 2001:173588 USPATFULL Full-text  
 TITLE: Thieno[2,3-d]pyrimidine-2,4-diones  
 INVENTOR(S): Bantick, John, Burton-on-the-Wolds, United Kingdom  
 Cooper, Martin, Loughborough, United Kingdom  
 Perry, Matthew, Loughborough, United Kingdom  
 Thorne, Philip, Loughborough, United Kingdom  
 PATENT ASSIGNEE(S): AstraZeneca AB, Sodertalje, Sweden (non-U.S.  
 corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6300334	B1	20011009
	WO 2000012514		20000309
APPLICATION INFO.:	US 1999-402837		19991013 (9)
	WO 1999-SE1400		19990818
			19991013 PCT 371 date
			19991013 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1998-2895	19980828
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Shah, Mukund J.	
ASSISTANT EXAMINER:	McKenzie, Thoams C.	
LEGAL REPRESENTATIVE:	Nixon & Vanderhye	
NUMBER OF CLAIMS:	12	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2510	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	Compounds of formula (I): ##STR1##	

wherein R.sup.1, R.sup.2, and R.sup.3 are defined in the specification. The compounds are useful for treating or reducing the risk of reversible obstructive airways disease.

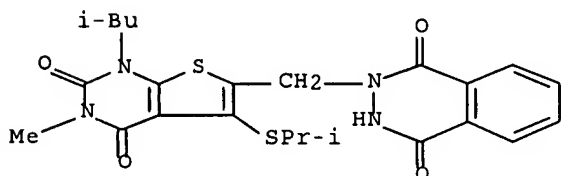
IT 259861-99-9P

(target compound; preparation of thieno[2,3-d]pyrimidine-2,4(1H,3H)-diones as

immunosuppressants)

RN 259861-99-9 USPATFULL

CN 1,4-Phthalazinedione, 2,3-dihydro-2-[[1,2,3,4-tetrahydro-3-methyl-5-[(1-methylethyl)thio]-1-(2-methylpropyl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl)methyl]- (9CI) (CA INDEX NAME)



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L99 ANSWER 35 OF 69 TOXCENTER COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:125146 TOXCENTER Full-text

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DOCUMENT NUMBER: CA12413176127Q

TITLE: Preparation of sulfamoylindanyl- and sulfamoyl-1,2,3,4-tetrahydronaphthylpyridazinone derivatives as drugs

AUTHOR(S): Ishida, Akihiko; Pponma, Koichi; Kono, Haruyuki; Tamura, Koji; Sasaki, Yasuhiko

CORPORATE SOURCE: ASSIGNEE: Tanabe Seiyaku Co

PATENT INFORMATION: JP 95233072 A2 5 Sep 1995

SOURCE: (1995) Jpn. Kokai Tokkyo Koho, 35 pp.

CODEN: JKXXAF.

COUNTRY: JAPAN

DOCUMENT TYPE: Patent

FILE SEGMENT: CAPLUS

OTHER SOURCE: CAPLUS 1996:52662

LANGUAGE: Japanese

ENTRY DATE: Entered STN: 16 Nov 2001

Last Updated on STN: 27 May 2003

ED Entered STN: 16 Nov 2001

Last Updated on STN: 27 May 2003

AB The title compds. [I; R1 = (un)substituted C1-10 alkyl, C3-6 cycloalkyl, lower alkenyl, (un)substituted heterocyclyl containing N, O, or S heteroatom, camphor-10-yl; R3 = H, (un)substituted lower alkyl, lower alkenyl; or R1 and R3 are linked to each other at the termini to form a lower alkylene; R2 = H, (un)substituted lower alkyl, aryl, lower alkenyl; A-B = ethylene or vinylene optionally substituted by 1-2 groups selected from lower alkyl or Ph; n = 1,2; D = H, halo], which are useful for the treatment and prevention of nephritis, in particular glomerulonephritis, IgA nephritis, nephrotic syndrome, and/or lupus nephritis and as blood platelet aggregation inhibitors and/or protective agents against endotoxin shock, are prepared Thus, 1.15 g 2-amino-5-[3-oxo-3(H)-4,5-dihydropyridazin-6-yl]indan was dissolved in EtOAc and THF, followed by successively adding an aqueous solution of 1.4 g K<sub>2</sub>CO<sub>3</sub> in 20 mL and 0.57 g MeSO<sub>2</sub>Cl, and the resulting mixture was stirred for 2 h to give 1.08 g 2-methanesulfonylamino-5-[3-oxo-3(H)-4,5-dihydropyridazin-6-yl]indan (II). Mice was administered with II at 100 mg/kg p.o. and after 30 min treated with a solution of Escherichia coli-derived endotoxin (lipopolysaccharides) in physiol. saline at 100 mg/10 mL/kg i.p. The survival ratio of the treated mice was 100 %.

CC 28-15

ST Miscellaneous Descriptors

sulfamoylindanylpyridazinone prepn treatment nephritis;  
sulfamoyltetrahydronaphthylpyridazinone prepn treatment nephrotic syndrome; glomerulonephritis treatment sulfamoylindanylpyridazinone; IgA nephritis treatment sulfamoylindanylpyridazinone; lupus nephritis treatment sulfamoylindanylpyridazinone; blood platelet aggregation inhibitor sulfamoylindanylpyridazinone; endotoxin shock protection sulfamoylindanylpyridazinone; indanylpyridazinone sulfamoyl prepn treatment nephritis; naphthylpyridazinone sulfamoyl prepn treatment nephrotic syndrome; pyridazinone sulfamoyl indanyl prepn treatment nephritis

RN 74-88-4 (Methyl iodide)

75-36-5 (Acetyl chloride)

75-86-5 (Acetone cyanohydrin)

79-30-1 (2-Methylpropanoyl chloride)

85-44-9 (Phthalic anhydride)  
 96-32-2 (Methyl bromoacetate)  
 100-39-0 (Benzyl bromide)  
 100-52-7 (Benzaldehyde)  
 103-80-0 (Phenylacetyl chloride)  
 105-36-2 (Ethyl bromoacetate)  
 106-65-0 (Dimethyl succinate)  
 107-08-4 (Propyl iodide)  
 107-99-3 (2-Dimethylaminoethyl chloride)  
 108-30-5 (Succinic anhydride)  
 108-90-7 (Chlorobenzene)  
 123-38-6 (Propanal)  
 124-63-0 (Methanesulfonyl chloride)  
 677-25-8 (Vinylsulfonyl fluoride)  
 1490-25-1 (Methyl succinyl chloride)  
 1622-32-8 (2-Chloroethanesulfonyl chloride)  
 1633-82-5 (3-Chloropropanesulfonyl chloride)  
 2386-60-9 (n-Butanesulfonyl chloride)  
 2975-41-9 (2-Aminoindan)  
 3099-31-8 (3-Picolyl chloride)  
 3144-16-9 ((+)-Camphorsulfonic acid)  
 3878-55-5 (Methyl hydrogen succinate)  
 7803-57-8 (Hydrazine hydrate)  
 10147-36-1 (Propanesulfonyl chloride)  
 16629-19-9 (2-Thiophenesulfonyl chloride)  
 79686-90-1 (2-Methoxycarbonylamino succinic anhydride)  
 138006-38-9 (2-Propionylaminoindan)  
 64624-93-7 (2-Propylindan)  
 155719-25-8 (2-Butanesulfonylaminoindan)

RN 155718-08-4; 155718-25-5; 155718-33-5; 155718-34-6; 155718-80-2;  
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'IBIB' IS NOT A VALID FORMAT

'ED' IS NOT A VALID FORMAT

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L99 ANSWER 36 OF 69 CHEMINFORMRX COPYRIGHT 2006 FIZ CHEMIE on STN

AN 200409129 CHEMINFORMRX Full-text

TI Regioselective Reduction of 2-(Arylideneamino)isoindole-1,3-diones -  
Synthesis of Alkaloid Analogues by N-Acylhydrazonium Ion Aromatic  
 $\pi$ -Cyclization.

AU FOGAIN-NINKAM, A.; DAICH, A.; DECROIX, B.; NETCHITAILO, P.

CS URCOM, Univ. Le Havre, F-76058 Le Havre, Fr.

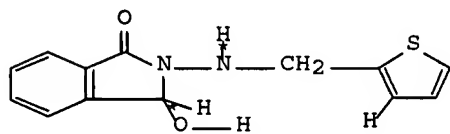
SO Eur. J. Org. Chem. (21), 4273-4278 (2003)

CODEN: EJOCFK ISSN: 1434-193X

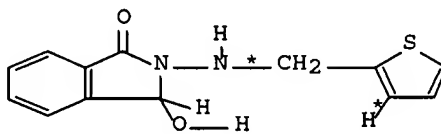
LA English

AB In the presence of NaBH<sub>3</sub>CN, 2-(arylideneamino)isoindole-1,3-diones undergo regioselective reduction yielding hydrazines like (IV) and (IX). Subsequent reaction with methanolic NaBH<sub>4</sub> at 5°C results in regioselective formation of hydroxylactams such as (V) and (XII). Treatment of the latter or their acetoxy derivatives with acids leads to N-acylhydrazonium ions which smoothly undergo cyclization to fused pyridazines. Unexpectedly, starting from the hydroxylactams (Vb) and (Vc) thienylmethyl-substituted derivatives such as (IX) are obtained.

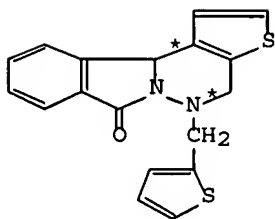
RX(12) OF 59 ...2 S ==> AA



V



V

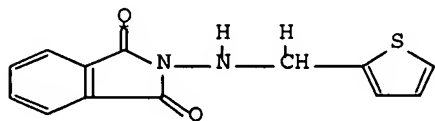
(12)  $\rightarrow$ 

IX  
YIELD 41.0%

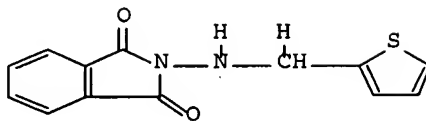
RX(12) RCT V, 996734  
RGT 219 (76-05-1), TFA  
PRO IX, 996738  
YDS 41.0 %  
T 25.0 Cel  
KW arylation; alkylation; C-alkylation  
NTE reaction: Vb  $\rightarrow$  IX

RX(32) OF 59 COMPOSED OF RX(8), RX(12)

RX(32) 2 0  $\Rightarrow$  AA

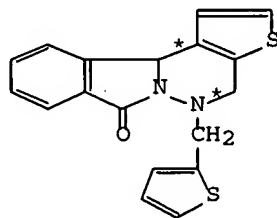


IV



IV

2  
STEPS  
 $\rightarrow$



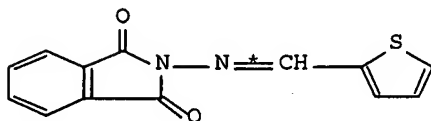
IX  
YIELD 41.0%

RX(8) RCT IV, 996731  
RGT 1156 (16940-66-2), NaBH<sub>4</sub>  
SOL 123 (67-56-1), MeOH  
PRO V, 996734  
YDS 71.0 %  
T 5.0 Cel  
KW addition; hydrogenation  
NTE reaction: IV  $\rightarrow$  V, example: 2  
RX(12) RCT V, 996734  
RGT 219 (76-05-1), TFA  
PRO IX, 996738

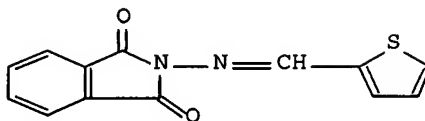
YDS 41.0 %  
 T 25.0 Cel  
 KW arylation; alkylation; C-alkylation  
 NTE reaction:Vb -> IX

RX(48) OF 59 COMPOSED OF RX(5), RX(8), RX(12)

RX(48) 2 F ==> AA

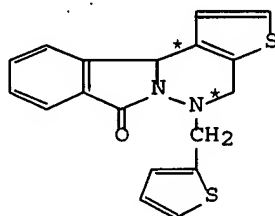


III



III

3  
 STEPS  
 →

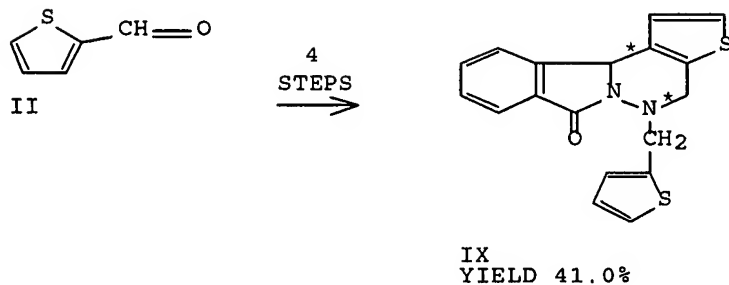
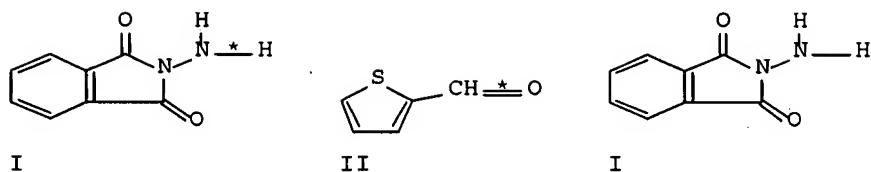


IX  
 YIELD 41.0%

RX(5) RCT III, 996729  
 RGT 430 (25895-60-7), NaBH3CN  
 103 (7647-01-0), HCl  
 SOL 123 (67-56-1), MeOH  
 PRO IV, 996731  
 YDS 74.0 %  
 T 10.0 - 25.0 Cel  
 KW addition; hydrogenation  
 NTE reaction:III -> IV, example: 2  
 RX(8) RCT IV, 996731  
 RGT 1156 (16940-66-2), NaBH4  
 SOL 123 (67-56-1), MeOH  
 PRO V, 996734  
 YDS 71.0 %  
 T 5.0 Cel  
 KW addition; hydrogenation  
 NTE reaction:IV -> V, example: 2  
 RX(12) RCT V, 996734  
 RGT 219 (76-05-1), TFA  
 PRO IX, 996738  
 YDS 41.0 %  
 T 25.0 Cel  
 KW arylation; alkylation; C-alkylation  
 NTE reaction:Vb -> IX

RX(49) OF 59 COMPOSED OF RX(2), RX(5), RX(8), RX(12)

RX(49) 2 A + 2 E ==> AA



RX(2) RCT I, 12345 (1875-48-5)  
 II, 12824 (98-03-3)  
 SOL 214 (108-88-3), toluene  
 CAT 517 (104-15-4), TosOH  
 PRO III, 996729  
 YDS 83.0 %  
 T.KW REFLUX  
 NTE reaction:I (II) -> III, example: 2

RX(5) RCT III, 996729  
 RGT 430 (25895-60-7), NaBH<sub>3</sub>CN  
 103 (7647-01-0), HCl  
 SOL 123 (67-56-1), MeOH  
 PRO IV, 996731  
 YDS 74.0 %  
 T 10.0 - 25.0 Cel  
 KW addition; hydrogenation  
 NTE reaction:III -> IV, example: 2

RX(8) RCT IV, 996731  
 RGT 1156 (16940-66-2), NaBH<sub>4</sub>  
 SOL 123 (67-56-1), MeOH  
 PRO V, 996734  
 YDS 71.0 %  
 T 5.0 Cel  
 KW addition; hydrogenation  
 NTE reaction:IV -> V, example: 2

RX(12) RCT V, 996734  
 RGT 219 (76-05-1), TFA  
 PRO IX, 996738  
 YDS 41.0 %  
 T 25.0 Cel  
 KW arylation; alkylation; C-alkylation  
 NTE reaction:Vb -> IX

=&gt; d bib ab hit 37

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE, DRUGU, MARPAT' - CONTINUE? (Y)/N:y

L99 ANSWER 37 OF 69 CHEMINFORMRX COPYRIGHT 2006 FIZ CHEMIE on STN

AN 200325164 CHEMINFORMRX Full-text

TI Pyridazinones as Selective Cyclooxygenase-2 Inhibitors.

AU LI, C. S.; ET AL.

CS Merck Frosst Cent. Ther. Res., Pointe-Claire-Dorval, Que. H9R 4P8, Can.

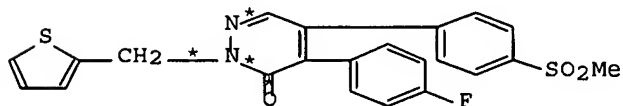
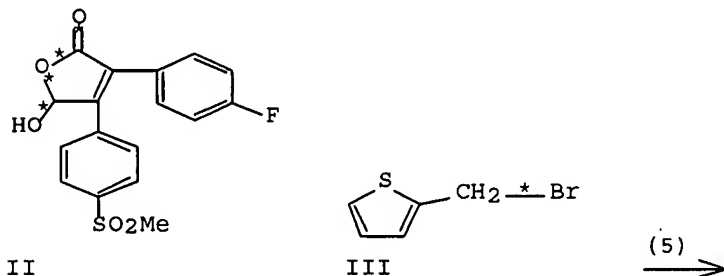
SO Bioorg. Med. Chem. Lett., 13(4), 597-600 (2003)

CODEN: BMCLE8 ISSN: 0960-894X

LA English

AB The preparation of title compounds such as (VI) and (XIII) following simple reaction pathways and evaluation of their structure-activity relationship as a new class of orally active COX-2 inhibitors based on the six-membered heterocyclic pyridazinone system are reported. Two potent and selective COX-2 inhibitors (VI) and (XIII) are identified.

RX(5) OF 21 ...H + P ==&gt; Q



YIELD 30.0-75.0%

RX(5) RCT II, 953532

III, 151272 (45438-73-1)

STAGE(1)

RGT 582 (302-01-2), H<sub>2</sub>N-NH<sub>2</sub>

STAGE(2)

RGT 1159 (1310-73-2), NaOH

SOL 76 (68-12-2), DMF

PRO IV, 953535

YDS 30.0 - 75.0 %

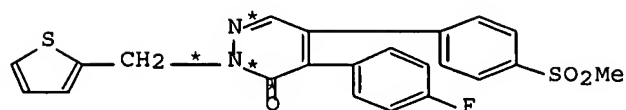
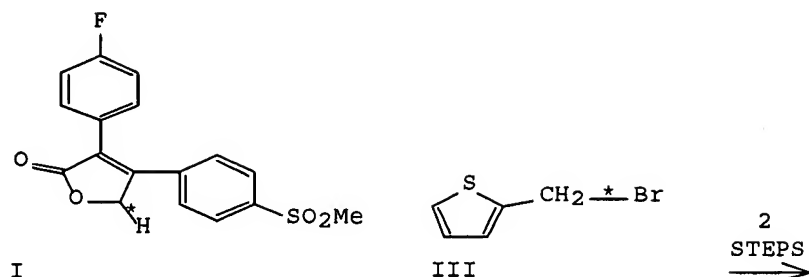
KW acylation; N-acylation; alkylation; N-alkylation

NTE reaction:II 2.(III) -&gt; IV, example: 3

10/518,503

RX(14) OF 21 COMPOSED OF RX(2), RX(5)

RX(14) G + P ==> Q



IV  
YIELD 30.0-75.0%

RX(2) RCT I, 953531

STAGE(1)

RGT 1135 (128-08-5), NBS

STAGE(2)

RGT 3 (64-19-7), AcOH

SOL 206 (109-99-9), THF

222 (7732-18-5), H2O

PRO II, 953532

YDS 45.0 %

KW alkylation; O-alkylation

NTE reaction:I -> II, example: 2

RX(5) RCT II, 953532

III, 151272 (45438-73-1)

STAGE(1)

RGT 582 (302-01-2), H2N-NH2

STAGE(2)

RGT 1159 (1310-73-2), NaOH

SOL 76 (68-12-2), DMF

PRO IV, 953535

YDS 30.0 - 75.0 %

KW acylation; N-acylation; alkylation; N-alkylation

NTE reaction:II 2.(III) -> IV, example: 3

=> d iall abeq tech abex hitstr 38-42

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE, DRUGU, MARPAT' - CONTINUE? (Y)/N:y

10/518,503

ACCESSION NUMBER: 2004-603388 [58] WPIX  
 CROSS REFERENCE: 1999-190573; 2000-350672; 2002-279861; 2002-361139;  
 2004-069781  
 DOC. NO. CPI: C2004-218616 [58]  
 TITLE: New pyridazinone compounds are cyclooxygenase-2  
 inhibitors used for treating e.g. rheumatoid arthritis,  
 fever and inflammation  
 DERWENT CLASS: B02; B03  
 INVENTOR: BASHA A; BLACK L A; COGHLAN M J; KOLASA T; KORT M E; LIU  
 H; MCCARTY C M; PATEL M; ROHDE J J; STEWART A O  
 PATENT ASSIGNEE: (BASH-I) BASHA A; (BLAC-I) BLACK L A; (COGH-I) COGHLAN M  
 J; (KOLA-I) KOLASA T; (KORT-I) KORT M E; (LIUH-I) LIU H;  
 (MCCA-I) MCCARTY C M; (PATE-I) PATEL M; (ROHD-I) ROHDE J  
 J; (STEW-I) STEWART A O; (ABBO-C) ABBOTT LAB  
 COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20040158064	A1	20040812	(200458)*	EN	158	[0]
US 7115591	B2	20061003	(200665)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20040158064	A1 Provisional	US 1997-56733P	19970822
US 20040158064	A1 CIP of	US 1998-129570	19980805
US 20040158064	A1 CIP of	US 1998-179605	19981027
US 20040158064	A1 CIP of	US 1999-261872	19990303
US 20040158064	A1 Div Ex	US 1999-427768	19991027
US 20040158064	A1 Div Ex	US 2001-871195	20010531
US 20040158064	A1	US 2003-464928	20030619

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 20040158064	A1 Div ex	US 6307047 B

PRIORITY APPLN. INFO: US 2003-464928 20030619  
 US 1997-56733P 19970822  
 US 1998-129570 19980805  
 US 1998-179605 19981027  
 US 1999-261872 19990303  
 US 1999-427768 19991027  
 US 2001-871195 20010531

INT. PATENT CLASSIF.:

IPC ORIGINAL: A61K0031-50 [I,A]; A61K0031-675 [I,A]; C07D0237-00 [I,C];  
 C07D0237-16 [I,A]; C07F0009-00 [I,C]; C07F0009-6509 [I,A]  
 IPC RECLASSIF.: C07D0237-00 [I,C]; C07D0237-14 [I,A]; C07D0405-00 [I,C];  
 C07D0405-04 [I,A]; C07D0409-00 [I,C]; C07D0409-04 [I,A]

BASIC ABSTRACT:

US 20040158064 A1 UPAB: 20050531  
 NOVELTY - Pyridazinone compounds (I), are new.  
 DETAILED DESCRIPTION - Pyridazinone compounds of formula (I) and their  
 salts, esters and prodrugs are new.  
 X = O, S, NR4, NORa or NNRbRc;

R4 = alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, arylalkyl, cycloalkenylalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

Ra-Rc = alkyl, cycloalkyl, aryl or arylalkyl;

R = alkyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyhaloalkyl, alkoxyiminoalkoxy, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylhaloalkyl, arylalkynyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkenyl, heterocyclyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylloxy, hydroxyalkyl, hydroxyiminoalkyl, (CH<sub>2</sub>)<sub>n</sub>C(O)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(OH)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>C(NORd)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(NORd)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(NRdRe)R<sub>5</sub>, R<sub>6</sub>R<sub>7</sub>, (CH<sub>2</sub>)<sub>n</sub>CCR<sub>7</sub>, (CH<sub>2</sub>)<sub>n</sub>(CH((CX')<sub>3</sub>)<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub>, (CH<sub>2</sub>)<sub>n</sub>(C(C(X')<sub>2</sub>)<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub> or (CH<sub>2</sub>)<sub>n</sub>(CHX')<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub>;

R<sub>5</sub> = T, haloalkenyl or haloalkynyl;

T = H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, arylalkyl, haloalkyl, heterocyclyl or heterocyclylalkyl;

R<sub>6</sub> = alkenylene or alkylene (both optionally substituted by halo);

R<sub>7</sub>, Rd, Re = T;

X' = halo;

m = 0-5;

n, p = 0-10;

R<sub>1</sub>-R<sub>3</sub> = H, alkenyl, cycloalkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, cycloalkyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkynyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halo, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y or W;

W = a group of formula (i) or (ii);

X<sub>1</sub> = S(O)<sub>2</sub>, S(O)(NR<sub>10</sub>), S(O), Se(O)<sub>2</sub>, P(O)(OR<sub>11</sub>) or P(O)(NR<sub>12</sub>R<sub>13</sub>);

X<sub>2</sub> = H, alkenyl, cycloalkenyl, alkyl, cycloalkyl, alkynyl or halo;

R<sub>9</sub> = alkenyl, alkoxy, alkyl, alkylamino, dialkylamino, alkylcarbonylamino, alkynyl, amino, NHH<sub>2</sub> or NCHN(R<sub>10</sub>R<sub>11</sub>);

R<sub>10</sub>-R<sub>13</sub> = H, alkyl or cycloalkyl, or

NR<sub>12</sub>R<sub>13</sub> = 3-6 membered ring containing 1 or 2 O, S or NR<sub>7</sub> heteroatoms;

Y = OR<sub>14</sub>, SR<sub>14</sub>, C(R<sub>16</sub>)(R<sub>17</sub>)R<sub>14</sub>, C(O)R<sub>14</sub>, C(O)OR<sub>14</sub>, N(R<sub>16</sub>)C(O)R<sub>14</sub>, NC(R<sub>16</sub>)R<sub>14</sub> or N(R<sub>16</sub>)R<sub>14</sub>;

R<sub>14</sub> = H, alkenyl, cycloalkenyl, alkoxyalkyl, alkyl, cycloalkyl, alkylthioalkyl, alkynyl, cycloalkenylalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl or NR<sub>18</sub>R<sub>19</sub>, and

R<sub>16</sub>-R<sub>19</sub> = H, alkenyl, cycloalkenyl, alkoxy, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl.

INDEPENDENT CLAIMS are also included for:

(1) preparation of (I: R<sub>2</sub> = (i); X<sub>2</sub> = H); and

(2) regioselective preparation of a 4,5-disubstituted pyridazinone which comprises treating a compound of formula (II) with a nucleophilic agent to displace the X<sub>a</sub> group, converting the OR<sub>98</sub> to a leaving group and treating the compound with a second nucleophilic agent.

X<sub>a</sub> = a leaving group, and

R<sub>98</sub> = alkyl or aryl.

ACTIVITY - Analgesic; Antipyretic; Antiinflammatory; Antirheumatic; Antiarthritic; Osteopathic; Cytostatic; Gynecological; Antiasthmatic; Tocolytic.

MECHANISM OF ACTION - Cyclooxygenase-2 (COX-2) inhibitor; Prostaglandin endoperoxide H synthase 2 inhibitor; Prostaglandin biosynthesis inhibitor. 2-(5-Methylthien-2-ylmethyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia) was tested for inhibition of in vitro biosynthesis of prostaglandin by recombinant human COX-1 (r-hu COX-1) and recombinant human COX-2 (r-hu COX-2) enzyme assays. (Ia) Was dissolved in dimethyl sulfoxide

(3.3 volume%) and preincubated with microsomes from r-hu COX-1 and r-hu COX-2 expressed in baculovirus/Sf9 cell system, together with cofactors phenol (2 mM) and hematin (1 micro-M) for 60 minutes prior to addition of arachidonic acid (10 micro-M). The reaction was run for 2.5 minutes at room temperature, then quenched with HCl and neutralized with NaOH. Prostaglandin E2 production in the presence and absence of (Ia) was determined by enzyme immunoassay and IC50 was calculated. (Ia) Showed IC50 (in micro-M) and inhibition (in %) of r-hu COX-1/r-hu COX-2 of 100/1 and 8/100, respectively.

USE - Used for treating pain, fever, inflammation, rheumatoid arthritis, osteoarthritis and cancer (claimed), dysmenorrhea, asthma, premature labor, adhesion (e.g. pelvic adhesions), ankylosing spondylitis and other inflammatory diseases.

ADVANTAGE - (I) Are selective cyclooxygenase-2 (COX-2) inhibitors, which is an inducible isoform associated with inflammation, compared to COX-1, a constitutive isoform, required as a housekeeping enzyme in many tissues. Unwanted gastrointestinal and renal side effects, associated with the current non-steroidal antiinflammatory drugs (NSAID), are minimized.

MANUAL CODE: CPI: B05-B01D; B05-B01E; B07-D10; B14-C01; B14-C03; B14-C04; B14-C06; B14-C09; B14-D05C; B14-D10; B14-H01; B14-K01A; B14-L08; B14-N14; B14-P03; N01-A01; N07-D08A

#### TECH

ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I: R2 = (i); X2 = H;) comprises reacting (I: R = H) with an alkylating agent.

Preferred Compounds: The alkylating agent is of formula R99-Q.

Q = a leaving group, and

R99 = 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)propenyl, 4-(2-methyl)but-2-yl, 1-dichloropropen-3-yl, 2,2-dimethyl-3-oxo-4-butyl, 2,3,3,4,4,4-hexafluorobuten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, alpha-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluoromethoxybenzyl, 4-fluorobenzyl, 4-fluorophenyl, 2-trifluoromethylbenzyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluoromethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, 2-benzo(b)thienylmethyl, 3-benzothienacyl, 5-chlorothiazol-2-ylmethyl, 5-methylthiazol-2-ylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, quinolin-2-ylmethyl or fluoroquinolin-2-ylmethyl.

ABEX ADMINISTRATION - The dosage is 0.001-1000 (preferably 0.1-100, especially 0.01-10) mg/kg/day orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically, buccally or by inhalation (with an oral or nasal spray).

SPECIFIC COMPOUNDS - 616 Compounds (I) are specifically claimed e.g.

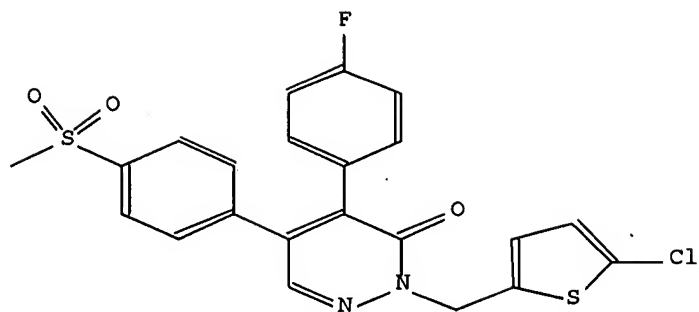
2-(5-methylthien-2-ylmethyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia).

EXAMPLE - To a solution of nitrogen-unsubstituted 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (0.465mmol), K2CO3 (1.4 mmol), 2-(bromomethyl)-5-methylthiophene (0.7 mmol) and NaI (catalytic) in anhydrous N,N-dimethylformamide (DMF) (10 ml) was stirred at room temperature for 18 hours. The reaction was then quenched with 2N HCl and worked up to give 2-(5-methylthien-2-ylmethyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia).

AN.S DCR-285364

CN.S 2-(5-Chloro-thiophen-2-ylmethyl)-4-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one

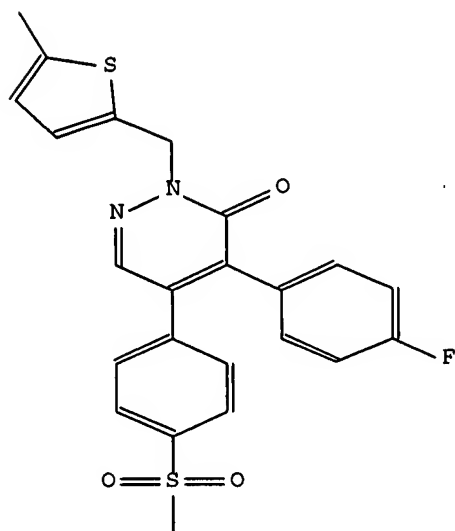
SDCN RA1RZ6



AN.S DCR-528585

CN.S 4-(4-Fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2-(5-methyl-thiophen-2-ylmethyl)-2H-pyridazin-3-one

SDCN RA6SZ8



L99 ANSWER 39 OF 69

ACCESSION NUMBER:

CROSS REFERENCE:

DOC. NO. CPI:

TITLE:

DERWENT CLASS:

INVENTOR:

PATENT ASSIGNEE:

WPIX COPYRIGHT 2006

THE THOMSON CORP on STN

2004-069781 [07] WPIX

1999-190573; 2000-350672; 2002-279861; 2002-361139;

2004-603388

C2004-028957 [07]

New pyridazinone compounds useful for treating e.g. pain, fever, inflammation, rheumatic arthritis and osteoarthritis

B02; B03

BASHA A; BLACK L A; COGHLAN M J; KOLASA T; KORT M E; LIU H; MCCARTY C M; PATEL M; ROHDE J J; STEWART A O

(BASH-I) BASHA A; (BLAC-I) BLACK L A; (COGH-I) COGHLAN M J; (KOLA-I) KOLASA T; (KORT-I) KORT M E; (LIUH-I) LIU H; (MCCA-I) MCCARTY C M; (PATE-I) PATEL M; (ROHD-I) ROHDE J

10/518,503

COUNTRY COUNT: J; (STEW-I) STEWART A O; (ABBO-C) ABBOTT LAB  
1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20030225276	A1	20031204	(200407)*	EN	160[0]	C07D403-02
US 7001895	B2	20060221	(200615)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20030225276	A1	Provisional	US 1997-56733P 19970822
US 20030225276	A1	CIP of	US 1998-129570 19980805
US 20030225276	A1	CIP of	US 1998-179605 19981027
US 20030225276	A1	CIP of	US 1999-261872 19990303
US 20030225276	A1	Div Ex	US 1999-427768 19991027
US 20030225276	A1	Div Ex	US 2001-870838 20010531
US 20030225276	A1		US 2003-417959 20030417

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 20030225276	A1 Div ex	US 6307047 B

PRIORITY APPLN. INFO: US 2003-417959 20030417  
US 1997-56733P 19970822  
US 1998-129570 19980805  
US 1998-179605 19981027  
US 1999-261872 19990303  
US 1999-427768 19991027  
US 2001-870838 20010531

INT. PATENT CLASSIF.:

MAIN: C07D403-02  
SECONDARY: C07F009-6509  
IPC ORIGINAL: A61K0031-50 [I,A]; A61K0031-675 [I,A]; C07D0237-00 [I,C];  
C07D0237-16 [I,A]

BASIC ABSTRACT:

US 20030225276 A1 UPAB: 20050528  
NOVELTY - Pyridazinone compounds (I), their salts, esters or prodrugs are new.  
DETAILED DESCRIPTION - Pyridazinone compounds of formula (I), their salts, esters or prodrugs are new.  
X = O, S, NR<sub>4</sub>, NOR<sub>5a</sub>, or NNR<sub>bRc</sub>;  
R<sub>4</sub> = alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic or heterocyclic alkyl;  
Ra-Rc = alkyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl;  
R = alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(OH)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>C(NOR<sub>d</sub>)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(NOR<sub>d</sub>)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(NR<sub>dRe</sub>)R<sub>5</sub>, -

R6R7, -(CH<sub>2</sub>)<sub>n</sub>C triple bond CR7, -(CH<sub>2</sub>)<sub>n</sub>(CH(CX'3))<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R7, -(CH<sub>2</sub>)<sub>n</sub>(CX'2)<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R7, or (CH<sub>2</sub>)<sub>n</sub>(CHX')<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R7;

R5 = H, (halo)alkenyl, (halo)alkyl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkynyl, heterocyclic, or heterocyclic alkyl;  
R6 = alkenylene or alkylene (both optionally substituted by halo);  
R7, Rd, Re = H, (cyclo)alkenyl, (halo)alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, heterocyclic or heterocyclic alkyl;

X' = halo;

m = 0-5;

n, p = 0-10;

R1-R3 = H, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkynyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halo, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y or W;

W = X1-R9-benzene (substituted by X2) or thiophene (substituted by X2 and at 2-position by X1-R9);

X1 = S(O)<sub>2</sub>, S(O)(NR10), S(O), Se(O)<sub>2</sub>, P(O)(OR11), or P(O)NR12R13;

X2 = H, alkenyl, alkyl, alkynyl or halo;

R9 = (cyclo)alkenyl, alkoxy, (cyclo)alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, dialkylamino, NHHN2, or -NCHNR10R11;

R10-R13 = H, alkyl, or cycloalkyl; or

NR12R13 = 3-6 membered ring containing 1-2 O, S, or NR7;

Y = OR14, SR14, CR16R17R14, C(O)R14, C(O)OR14, NR16C(O)R14, NCR16R14, or NR16R14;

R14 = H, (cyclo)alkenyl, alkoxyalkyl, (cyclo)alkyl, alkylthioalkyl, alkynyl, cycloalkenylalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, or NR18R19; and

R16-R19 = H, (cyclo)alkenyl, alkoxy, (cyclo)alkyl, aryl, arylalkyl, heterocyclic, or heterocyclic alkyl;

provided that one (and only one) of R1-R3 = W.

INDEPENDENT CLAIMS are also included for:

(1) preparation of pyridazinone derivative of formula (II) involving reacting (II; R = H) with an alkylating agent (preferably a compound of formula R'9-Q); and

(2) preparation of 4,5-disubstituted pyridazinone either involving:

(a) reacting 2H-pyridazin-3-one derivative of formula (III) with a nucleophilic agent to displace the X group;

(b) converting the -OR98 to a leaving group; and

(c) reacting (III) with a second nucleophilic agent, or reacting 4-phenyl-5H-furan-2-one derivative of formula (IV) with a hydrazine of formula RNHNH2.

R99 = alkenyl, alkoxy, alkyl, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, -NHHN2 or -NCHNR10R11;

R98 = alkyl or aryl;

Q = leaving group; and

R'9 = methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,2-dimethyl-3-oxo-4-butyl, 2,3,3,4,4,4-hexafluorobuten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, alpha-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluoromethoxyphenacyl, 4-fluorobenzyl, 4-fluorophenyl, 2-trifluoromethylbenzyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluoromethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, 2-benzo(b)thienylmethyl, 3-benzothienacyl, 5-chlorothiazol-2-ylmethyl, 5-methylthiazol-2-ylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, quinolin-2-ylmethyl, or

fluoroquinolin-2-ylmethyl (preferably 1,1,1-trifluoroethyl, benzyl, or 4-fluorophenyl).

ACTIVITY - Analgesic; Antipyretic; Antiinflammatory; Antirheumatic; Antiarthritic; Osteopathic; Cytostatic.

MECHANISM OF ACTION - Cyclooxygenase-2 (COX-2) Inhibitor; Prostaglandin Biosynthesis (preferably PGHS-1 and PGHS-2) Inhibitor.

In vitro prostaglandin biosynthesis inhibitory activity of 2-(4-fluorobenzyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia) was evaluated using recombinant human COX-2 enzyme assay. (Ia) in dimethylsulfoxide was preincubated with microsomes from recombinant human PGHS-1 or PGHS-2 expressed in the baculovirus/Sf9 cell system as described in Gierse, J. K., Hauser, S. D., Creely, D. P., Koboldt, C., Rangwala, S., H., Isakson, P. C., and Seibert, K. Expression and selective inhibition of the constitutive and inducible forms of cyclooxygenase, *Biochem J.* 1995, 305: 479. (Ia) Inhibited prostaglandin biosynthesis with an IC<sub>50</sub> of 10 nM.

USE - For treating pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions and cancer (claimed).

ADVANTAGE - The compounds are potent inhibitors of cyclooxygenase-2 and PGHS-2. The selectivity of the compounds for COX-2 minimizes the unwanted gastrointestinal tract and renal side-effects as compared to non-steroidal antiinflammatory drugs. MANUAL CODE: CPI: B05-B01D; B05-B01E; B05-B01J; B05-B01M; B06-H;

B07-D13; B14-C01; B14-C03; B14-C04; B14-C09; B14-D05C; B14-F04; B14-F07; B14-H01B; B14-L08

#### TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I; R<sub>2</sub> = X1-R9-benzene (substituted by X2)) involves reacting (I; R = H) with an alkylating agent.

ABEX DEFINITIONS - Preferred Definitions: - R<sub>2</sub> = W; - W = -X1-R9-benzene (substituted by X2); - X = O; - X1 = S(O)<sub>2</sub>; - R<sub>9</sub> = NH<sub>2</sub>; - X<sub>2</sub> = H; - R = t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-fluorophenyl, or 2,2,2-trifluoroethyl; - R<sub>1</sub> = isobutoxy, isopentyloxy, (3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propoxy, 3-hydroxy-3-methylbutoxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluorophenyl, 4-fluorophenyl or Y; - Y = OR<sub>14</sub>; - R<sub>14</sub> = aryl; and - R<sub>3</sub> = H.

ADMINISTRATION - Administration of (I) is 0.001-1000, preferably 0.1-100 mg/kg/day orally, 0.01-10 mg/kg/day parenterally, or rectally, vaginally, topically, transdermally, intraperitoneally, buccally, or nasally.

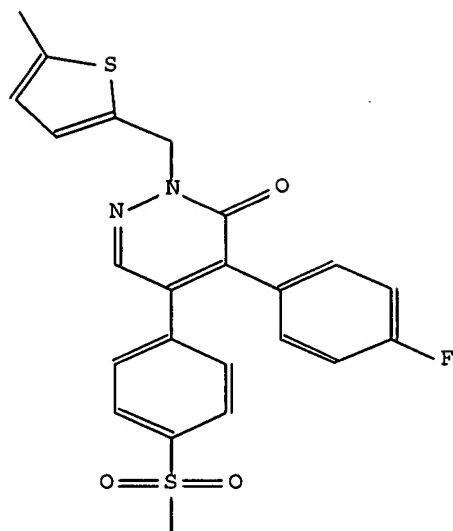
SPECIFIC COMPOUNDS - 634 Compounds (I) are specifically claimed, e.g. 2-(4-fluorobenzyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia).

EXAMPLE - A solution of 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (160 mg), potassium carbonate (193 mg), 4-fluorobenzylbromide (0.09 ml) and sodium iodide in anhydrous N,N-dimethylformamide (10 ml) were stirred at room temperature for 18 hours. The reaction mixture was quenched with 2 N HCl, extracted with ethyl acetate (2 x 20 ml), washed with brine and water, dried, filtered and concentrated to give 2-(4-fluorobenzyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ia) (110 mg).

AN.S DCR-528585

CN.S 4-(4-Fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2-(5-methyl-thiophen-2-ylmethyl)-2H-pyridazin-3-one

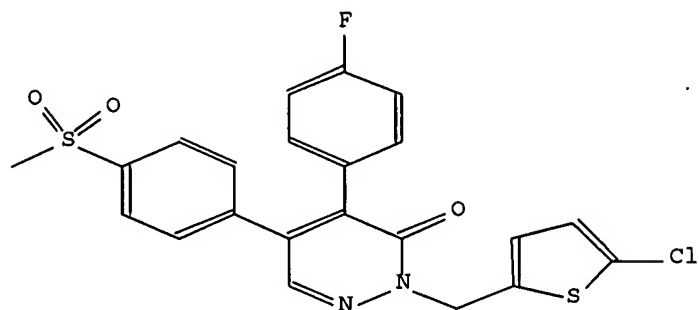
SDCN RA6SZ8



AN.S DCR-285364

CN.S 2-(5-Chloro-thiophen-2-ylmethyl)-4-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one

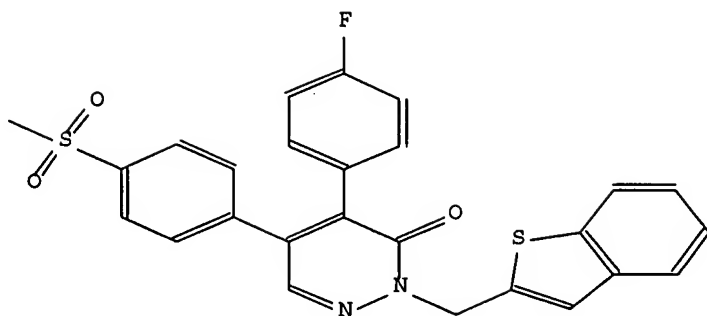
SDCN RA1RZ6



AN.S DCR-828750

CN.S 2-Benzo[b]thiophen-2-ylmethyl-4-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one

SDCN RACQNP



L99 ANSWER 40 OF 69 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2002-361139 [39] WPIX  
 CROSS REFERENCE: 1999-190573; 2000-350672; 2002-054478; 2002-279861;  
 2004-069781; 2004-603388  
 DOC. NO. CPI: C2002-102182 [39]  
 TITLE: New pyridazinone compounds, useful as selective  
 cyclooxygenase-2 inhibitors for treating pain, fever,  
 inflammation, rheumatoid arthritis, osteoarthritis,  
 adhesions and cancer  
 DERWENT CLASS: B02; B03  
 INVENTOR: BASHA A; BLACK L A; COGHLAN M J; KOLASA T; KORT M E; LIU  
 H; MCCARTY C M; PATEL M; ROHDE J J; STEWART A O  
 PATENT ASSIGNEE: (BASH-I) BASHA A; (BLAC-I) BLACK L A; (COGH-I) COGHLAN M  
 J; (KOLA-I) KOLASA T; (KORT-I) KORT M E; (LIUH-I) LIU H;  
 (MCCA-I) MCCARTY C M; (PATE-I) PATEL M; (ROHD-I) ROHDE J  
 J; (STEW-I) STEWART A O  
 COUNTRY COUNT: 1

## PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20020028938	A1	20020307	(200239)*	EN	159[0]	C07D403-02

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20020028938	A1	Provisional	US 1997-56733P 19970822
US 20020028938	A1	CIP of	US 1998-129570 19980805
US 20020028938	A1	CIP of	US 1998-179605 19981027
US 20020028938	A1	CIP of	US 1999-261872 19990303
US 20020028938	A1	Div Ex	US 1999-427768 19991027
US 20020028938	A1		US 2001-870838 20010531

PRIORITY APPLN. INFO: US 2001-870838 20010531  
 US 1997-56733P 19970822  
 US 1998-129570 19980805  
 US 1998-179605 19981027  
 US 1999-261872 19990303  
 US 1999-427768 19991027

## INT. PATENT CLASSIF.:

MAIN: C07D403-02  
 SECONDARY: C07D237-14

## BASIC ABSTRACT:

US 20020028938 A1 UPAB: 20050525

NOVELTY - Pyridazinone compounds (I) and their salts, esters, or prodrugs are new.

DETAILED DESCRIPTION - Pyridazinone compounds of formula (I) and their salts, esters, or prodrugs are new.

X = O, S, NR<sub>4</sub>, NOR<sub>a</sub> or NNR<sub>b</sub>R<sub>c</sub>;

R<sub>4</sub> = alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic or heterocyclic alkyl;

R<sub>a</sub>-R<sub>c</sub> = alkyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl;

R = alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxy-iminoalkoxy, (CH<sub>2</sub>)<sub>n</sub>C(O)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(OH)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>C(NOR<sub>d</sub>)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(NOR<sub>d</sub>)R<sub>5</sub>, (CH<sub>2</sub>)<sub>n</sub>CH(NR<sub>d</sub>Re)R<sub>5</sub>, R<sub>6</sub>R<sub>7</sub>, (CH<sub>2</sub>)<sub>n</sub>C=CR<sub>7</sub>, (CH<sub>2</sub>)<sub>n</sub>(CH(C(X')<sub>3</sub>))(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub>, (CH<sub>2</sub>)(C(X')<sub>2</sub>)<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub> or (CH<sub>2</sub>)<sub>n</sub>(CHX')<sub>m</sub>(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub>;

R<sub>5</sub> = H, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic or heterocyclic alkyl;

R<sub>6</sub> = alkenylene, alkylene, halo-substituted alkenylene or halo-substituted alkylene;

R<sub>7</sub> = H, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, or heterocyclic alkyl;

R<sub>d</sub>, R<sub>e</sub> = H, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, hetero- cyclic or heterocyclic alkyl;

X' = halo;

m = 0-5;

n = 0-10;

p = 0-10;

R<sub>1</sub>-R<sub>3</sub> = H, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkynyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halo, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y or W;

W = a group of formula (i) or (ii);

X<sub>1</sub> = S(O)<sub>2</sub> S(O) (NR<sub>10</sub>), S(O), Se(O)<sub>2</sub>, P(OR<sub>11</sub>) or P(O) (NR<sub>10</sub>R<sub>11</sub>);

X<sub>2</sub> = H, alkenyl, alkyl, alkynyl or halo;

R<sub>9</sub> = alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, NHNH<sub>2</sub> or NCHN(R<sub>10</sub>)R<sub>11</sub>;

R<sub>10</sub>-R<sub>13</sub> = H, alkyl or cycloalkyl; or

NR<sub>12</sub>R<sub>13</sub> = 3-6 membered ring containing 1-2 O, S or NR<sub>7</sub>;

Y = OR<sub>14</sub>, SR<sub>14</sub>, CR<sub>16</sub>R<sub>17</sub>, C(O)R<sub>14</sub>, C(O)OR<sub>14</sub>, N(R<sub>16</sub>)C(O)R<sub>14</sub>, NC(R<sub>16</sub>)R<sub>14</sub> or N(R<sub>16</sub>)R<sub>14</sub>;

R<sub>14</sub> = H, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl or NR<sub>18</sub>R<sub>19</sub>;

R<sub>16</sub>-R<sub>19</sub> = H, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic or heterocyclic alkyl;

provided that only one of R<sub>1</sub>-R<sub>3</sub> is W.

INDEPENDENT CLAIMS are included for:

(1) preparation of compounds of formula (I'); and

(2) methods of regioselectively preparing 4,5-disubstituted pyridazinones.

ACTIVITY - Analgesic; Antipyretic; Antiinflammatory; Antirheumatic; Antiarthritic; Osteopathic; Cytostatic; Antiasthmatic; Tocolytic; Gynecological.

MECHANISM OF ACTION - Selective cyclooxygenase-2 (COX-2) inhibitor; Prostaglandin biosynthesis inhibitor.

In an in vitro assay to examine the inhibition of prostaglandin biosynthesis using recombinant human COX-1 (r-hu COX-1) and COX-2 (r-hu COX-2), 2-phenyl-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)pyridazinone (Ia) at 10 micro M inhibited r-hu COX-2 by 97%. In comparison, (Ia) showed 0% inhibition of r-hu COX-1 at 100 micro M.

USE - For inhibiting prostaglandin biosynthesis, for treating pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer (all claimed). May also be useful for treating dysmenorrhea, asthma, premature labor, and in particular pelvic adhesions, osteoporosis, and ankylosing spondylitis.

ADVANTAGE - The selectivity of (I) avoids gastrointestinal side effects e.g. ulcers and bleeding and renal problems associated with non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, naproxen and fenemates which inhibit both COX-1 and COX-2. MANUAL CODE: CPI: B05-B01E; B05-B02C; B07-D10; B14-C01; B14-C03;

B14-C04; B14-C06; B14-C09; B14-D05C; B14-G02A; B14-H01; B14-K01A

#### TECH

ORGANIC CHEMISTRY - Preparation: In (1), preparation of (I') comprises treating a compound of formula (I'; R = H) with an alkylating agent. In (2), regioselective preparation of 4,5-disubstituted pyridazinones comprises:

- (a) treating a compound of formula (IV) with a nucleophilic agent to displace the X'' group;
- (b) converting the OR98 group to a leaving group; and
- (c) treating the product with a second nucleophilic agent to give a 4,5-disubstituted pyridazinone.

Regioselective preparation of 4,5-disubstituted pyridazinones may also comprise treating a compound of formula (V) with a hydrazine of formula RNHNH<sub>2</sub> to give pyridazinone compounds of formula (I').

R98 = alkyl or aryl; and

X'' = leaving group.

Preferred Compounds: (I) are preferably of formula (I''').

ABEX ADMINISTRATION - Administration of (I) is 0.001-1000 (preferably 0.1-100) mg/kg/day orally, or 0.01-10 mg/kg parenterally, in single or divided doses. (I) May also be administered parenterally, rectally, vaginally, topically or transdermally.

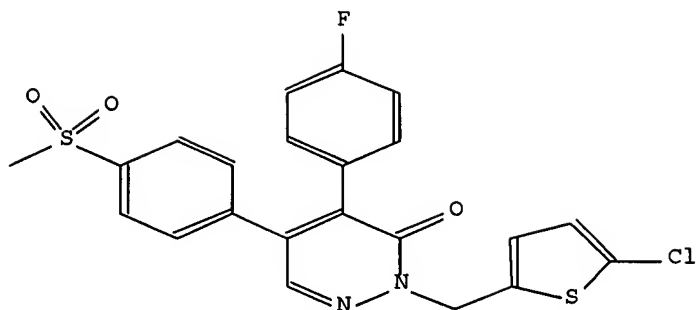
SPECIFIC COMPOUNDS - About 700 compounds (I) (including about 300 compounds (I''')) are specifically claimed, e.g. 2-phenyl-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)pyridazinone (Ia).

EXAMPLE - A solution of 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (160 mg), 4-fluorobenzylbromide (0.09 ml) and NaI (catalytic amount) in anhydrous dimethyl formamide (DMF; 10 ml) was stirred at room temperature for 18 hours. The reaction was quenched with 2 N HCl, extracted with ethyl acetate (2 x 20 ml) washed with brine and water, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by column chromatography (eluting with 2:2:6 ethyl acetate/dichloromethane/pentanes). Crystallization from ether/pentanes gave 2-(4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (Ib).

AN.S DCR-285364

CN.S 2-(5-Chloro-thiophen-2-ylmethyl)-4-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one

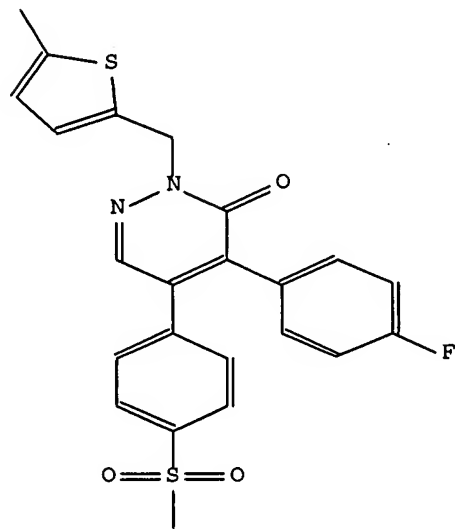
SDCN RA1RZ6



AN.S DCR-528585

CN.S 4-(4-Fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2-(5-methyl-thiophen-2-ylmethyl)-2H-pyridazin-3-one

SDCN RA6SZ8



L99 ANSWER 41 OF 69

ACCESSION NUMBER:

CROSS REFERENCE:

DOC. NO. CPI:

TITLE:

DERWENT CLASS:

INVENTOR:

PATENT ASSIGNEE:

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THE THOMSON CORP on STN

2002-279861 [32] WPIX

1999-190573; 2000-350672; 2002-054478; 2002-361139;  
2004-069781; 2004-603388

C2002-082271 [32]

New pyridazinones useful in the treatment of  
cyclooxygenase mediated diseases e.g. pain

B03

BASHA A; BLACK L A; COGHLAN M J; KOLASA T; KORT M E; LIU  
H; MCCARTY C M; PATEL M; ROHDE J J; STEWART A O(BASH-I) BASHA A; (BLAC-I) BLACK L A; (COGH-I) COGHLAN M  
J; (KOLA-I) KOLASA T; (KORT-I) KORT M E; (LIUH-I) LIU H;

10/518,503

(MCCA-I) MCCARTY C M; (PATE-I) PATEL M; (ROHD-I) ROHDE J  
J; (STEW-I) STEWART A O

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20020013318	A1	20020131	(200232)*	EN	159[0]	A61K031-50

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20020013318	A1	Provisional	US 1997-56733P 19970822
US 20020013318	A1	CIP of	US 1998-129570 19980805
US 20020013318	A1	CIP of	US 1998-179605 19981027
US 20020013318	A1	CIP of	US 1999-261872 19990303
US 20020013318	A1	Div Ex	US 1999-427768 19991027
US 20020013318	A1		US 2001-871195 20010531

PRIORITY APPLN. INFO: US 2001-871195 20010531  
US 1997-56733P 19970822  
US 1998-129570 19980805  
US 1998-179605 19981027  
US 1999-261872 19990303  
US 1999-427768 19991027

INT. PATENT CLASSIF.:

MAIN: A61K031-50  
SECONDARY: C07D237-14

BASIC ABSTRACT:

US 20020013318 A1 UPAB: 20050525  
NOVELTY - Pyridazinone derivatives (I) are new.  
DETAILED DESCRIPTION - Pyridazinones of formula (I), their salts, ester or prodrugs are new.  
X = O, S, -NR<sub>4</sub>, -NORa or -NNRbRc;  
R<sub>4</sub> = alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl or heterocyclic(alkyl);  
Ra, Rb and Rc = alkyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl;  
R = alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(OH)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>C(NORd)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(NORd)R<sub>5</sub>, -(CH<sub>2</sub>)<sub>n</sub>CH(NRdRe)R<sub>5</sub>, -R<sub>6</sub>R<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>CCR<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>(CH(CX'3))m(CH<sub>2</sub>)pR<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>(CX'2)-m(CH<sub>2</sub>)pR<sub>7</sub> or -(CH<sub>2</sub>)<sub>n</sub>(CHX')m(CH<sub>2</sub>)pR<sub>7</sub>;  
R<sub>5</sub> = R<sub>7</sub>, haloalkenyl or haloalkynyl;  
R<sub>6</sub> = alkenylene or alkylene (both optionally substituted by halogen);  
R<sub>7</sub>, Rd and Re = H, (cyclo)alkenyl, (cyclo)alkyl, alkynyl, aryl, arylalkyl, haloalkyl or heterocyclic(alkyl);  
X' = halogen;  
m = 0 - 5;  
n = 0 - 10;  
p = 0 - 10;  
R<sub>1</sub> - R<sub>3</sub> = H, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkynyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy, aminocarbonylalkyl, aryl,

arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y or W;

W = T'-X1-R9;

T' = 1,4-phenylene or 2,5-thiophenylene (both substituted by X2);

X1 = S(O)2, S(O)(NR10), S(O), Se(O)2, P(O)(OR11) or P(O)(NR12R13);

X2 = H, alkenyl, alkyl, alkynyl, halogen;

R9 = alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, -NHNH2 or -NCHN(R10)R11;

R10 - R13 = H or (cyclo)alkyl;

NR12R13 = 3 - 6 membered ring containing 1 or 2 heteroatoms selected from O, S or NR7;

Y = -OR14, -SR14, -C(R16)(R17)R14, -C(O)R14, -C(O)OR14, -N(R16)C(O)R14, -NC(R16)R14 or -N(R16)R14;

R14 = H, (cyclo)alkenyl, alkoxyalkyl, (cyclo)alkyl, alkylthioalkyl, alkynyl, cycloalkenylalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic(alkyl), hydroxyalkyl or NR18R19;

R16 - R19 = H, (cyclo)alkenyl, alkoxy, (cyclo)alkyl, aryl, arylalkyl or heterocyclic(alkyl).

provided that at least one (preferably only one) of R1 - R3 must be W. INDEPENDENT CLAIMS are also included for

(1) preparation of a compound of formula (III) by treating a compound of formula (III) (where R = H) with an alkylating agent;

(2) regioselective preparation of a 4,5-disubstituted pyridazinone involving either

(i) treating a compound of formula (IV) with a nucleophilic agent to displace the X' group;

(ii) converting the -OR98 to a leaving group; and

(iii) treating the compound with a second nucleophilic agent to form the 4,5-disubstituted pyridazinone, or treating a compound of formula (V) with a hydrazine of formula R'NHNH2; and

(3) a compound of formula (VI), its salt, ester or prodrug.

R'9 = (cyclo)alkenyl, alkoxy, (cyclo)alkyl, alkynyl, amino, dialkylamino, -NHNH2 or -NCHN(R10)R11;

R' = alkenyl, alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, aryloxyhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, -(CH2)nC(O)R'5, -(CH2)nCH(OH)R'5, -(CH2)nC(NORd)R'5, -(CH2)nCH(NORd)R'5, -(CH2)nCH(NRdRe)R'5, -R6R7, -(CH2)nCCR7, -(CH2)n(CH(CX'3))m(CH2)pR7, -(CH2)n(CX'2)m(CH2)pR7 or -(CH2)n(CHX')m(CH2)pR7;

R'5 = R5 (except H);

R'1 and R'3 = H, alkenyl, alkoxyalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, cyano, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic(alkyl), hydroxyalkoxy, hydroxyalkylamino, hydroxyalkylthio, mercaptoalkoxy, nitro or Y';

Y' = -OR'14, -SR'14, -C(R16)(R17)R'14, -C(O)R'14, -C(O)OR'14, -N(R16)C(O)R'14, -NC(R16)R'14 or -N(R16)R'14;

R'14 = R14 (except hydroxyalkyl).

R98 = alkyl or aryl;

X' = leaving group.

R = alkyl, aryl, arylalkyl, haloalkyl or haloalkenyl;

R1 = alkoxy, aminoalkylcarbonyloxyalkoxy, carboxyalkylcarbonyloxyalkoxy, hydroxyalkoxy, hydroxyalkyl or phosphonatoalkoxy;

R9 = alkyl, alkylcarbonylamino or amino.

ACTIVITY - Analgesic; antipyretic; antiinflammatory; antirheumatic; antiarthritic; osteopathic; cytostatic.

MECHANISM OF ACTION - Prostaglandin biosynthesis (particularly prostaglandin endoperoxide H synthase (PGHS-2, cyclooxygenase-2, COX-2) protein) inhibitor.

Carrageenan induced air pouch prostaglandin biosynthesis model (CAP) study was carried out on male sprague dawley rats by injecting 20 ml of sterile air on day 0. Three days later the pouch was reinflated with an additional 10 ml of sterile air. On day 7, 1 nanoliter of saline containing 0.2% lambda carrageenan was injected into the pouch to induce inflammatory reaction by the release of prostaglandins. 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone was dosed at 3 mg/kg body weight, 30 minutes prior to carrageenan. 4 hours after the carrageenan injection the pouch was lavaged and levels of prostaglandins determined. The result indicated 98% inhibition of prostaglandin biosynthesis by the test compound.

USE - For the treatment of pain, fever, inflammation, rheumatoid arthritis, osteoarthritis, adhesions and cancer (claimed). The compounds are also useful in the treatment of cyclooxygenase mediated diseases, premature labor, osteoporosis and ankylosing spondylitis.

ADVANTAGE - The compounds are selective inhibitors of PGHS-2, have no side-effects and minimize stomach toxicity. MANUAL CODE: CPI: B07-D13; B14-C01; B14-C03; B14-C04; B14-C09A;

B14-C09B; B14-D08; B14-H01; B14-N01; B14-N14

#### TECH

ORGANIC CHEMISTRY - Preferred Compounds: The alkylating agent is of formula R99-Q.

R99 = methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,2-dimethyl-3-oxo-4-butyl, 2,3,3,4,4,4-hexafluorobuten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, ortho-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluoromethoxyphenacyl, 4-fluorobenzyl, 4-fluorophenyl, 2-trifluoromethylbenzyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluoromethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylethyl, 2-benzo(b)thienylmethyl, 3-benzothienacyl, 5-chlorothiazol-2-ylmethyl, 5-methylthiazol-2-ylethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylethyl, quinolin-2-ylmethyl or fluoroquinolin-2-ylmethyl (preferably 1,1,1-trifluoroethyl, phenyl, benzyl, alpha-methyl-4-fluorobenzyl, 4-fluorobenzyl, 4-fluorophenyl or 2,4-difluorobenzyl, especially 1,1,1-trifluoroethyl, benzyl or 4-fluorophenyl);  
Q = leaving group.

ABEX DEFINITIONS - Preferred Definitions - R2 = W; - T' = 1,4-phenylene; - X1 = SO2; - R9 = methyl or amino; - X2 = H or fluorine (preferably H); - R = tert-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-fluorophenyl or 2,2,2-trifluoroethyl; - R1 = isobutoxy, isopentyloxy, (3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propoxy, 3-hydroxy-3-methylbutoxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluorophenyl, 4-fluorophenoxy or Y; - Y = -OR14; - R14 = aryl; - R3 = H; - R = tert-butyl, haloalkyl, phenyl (optionally mono- or di-substituted by chlorine or fluorine); - R1 = (hydroxy)alkoxy or phosphonatoalkoxy; - R'9 = methyl or amino.

ADMINISTRATION - The compounds are administered orally, subcutaneously,

intramuscularly, rectally, vaginally or transdermally. Dosage is 0.001 - 1000 (preferably 0.1 - 100) mg/kg body weight/day for oral administration.

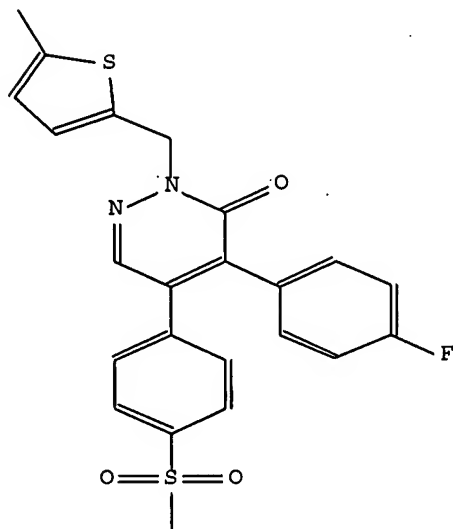
SPECIFIC COMPOUNDS - 621 compounds are specifically claimed as (I). e.g. 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone.

EXAMPLE - A mixture of 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)-3(2H)-pyridazinone (172 mg), Cu powder (32 mg), anhydrous K<sub>2</sub>CO<sub>3</sub> (207 mg) and 3,4-difluorobromobenzene (0.12 ml) was prepared in pyridine (20 ml). The solution was stirred at reflux for 14 hours. The mixture was then cooled and partitioned between water and ethyl acetate. The acetate layer was washed with 10% citric acid, water, brine and concentrated in vacuum to obtain 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-3(2H)-pyridazinone (yield 70%).

AN.S DCR-528585

CN.S 4-(4-Fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2-(5-methyl-thiophen-2-ylmethyl)-2H-pyridazin-3-one

SDCN RA6SZ8



L99	ANSWER 42 OF 69	WPIX COPYRIGHT 2006	THE THOMSON CORP on STN
ACCESSION NUMBER:	2001-488639 [53]	WPIX	
CROSS REFERENCE:	2001-465209; 2001-475871; 2001-514302; 2001-514303; 2001-514320; 2001-522009; 2002-352118		
DOC. NO. CPI:	C2001-146647 [53]		
TITLE:	Use of pyridazino quinolinedione compounds for treating a subject e.g. human suffering from pain, especially neuropathic pain		
DERWENT CLASS:	B02		
INVENTOR:	BARE T; BARE T M; BROWN D G; BROWN D G A; HORCHLER C L; HORCHLER C L A; MURPHY M; MURPHY M A; STEELMAN G B; STEELMAN G B A; URBANEK R A; URBANEK R A A; XIAO W; XIAO W A; BARE M		
PATENT ASSIGNEE:	(ASTR-C) ASTRAZENECA AB; (BARE-I) BARE T M; (BROW-I) BROWN D G; (HORC-I) HORCHLER C L; (MURP-I) MURPHY M;		

10/518,503

(STEE-I) STEELMAN G B; (URBA-I) URBANEK R A; (XIAO-I)  
XIAO W  
93

COUNTRY COUNT:

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001047924	A1	20010705	(200153)	*	EN 57 [0]	
AU 2001024200	A	20010709	(200164)		EN	
EP 1244660	A1	20021002	(200265)		EN	
JP 2003519146	W	20030617	(200349)	JA	77	C07D471-04
US 20030181449	A1	20030925	(200364)		EN	
EP 1244660	B1	20060322	(200622)		EN	
DE 60026883	E	20060511	(200634)		DE	
DE 60026883	T2	20061123	(200678)		DE	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001047924	A1	WO 2000-SE2607	20001219
DE 60026883	E	DE 2000-626883	20001219
EP 1244660	A1	EP 2000-987932	20001219
EP 1244660	B1	EP 2000-987932	20001219
DE 60026883	E	EP 2000-987932	20001219
EP 1244660	A1	WO 2000-SE2607	20001219
JP 2003519146	W	WO 2000-SE2607	20001219
US 20030181449	A1	WO 2000-SE2607	20001219
EP 1244660	B1	WO 2000-SE2607	20001219
DE 60026883	E	WO 2000-SE2607	20001219
AU 2001024200	A	AU 2001-24200	20001219
JP 2003519146	W	JP 2001-549394	20001219
US 20030181449	A1	US 2003-168761	20030224
DE 60026883	T2	DE 2000-626883	20001219
DE 60026883	T2	EP 2000-987932	20001219
DE 60026883	T2	WO 2000-SE2607	20001219

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 60026883	E	EP 1244660
AU 2001024200	A	WO 2001047924
EP 1244660	A1	WO 2001047924
JP 2003519146	W	WO 2001047924
EP 1244660	B1	WO 2001047924
DE 60026883	E	WO 2001047924
DE 60026883	T2	EP 1244660
DE 60026883	T2	WO 2001047924

PRIORITY APPLN. INFO: US 2000-236881P 20000929  
US 1999-171906P 19991223  
US 2003-168761 20030224

INT. PATENT CLASSIF.:

MAIN: C07D471-04  
SECONDARY: A61K031-5025; A61K031-5377; A61P025-04  
IPC ORIGINAL: A61K0031-5025 [I,A]; A61K0031-5025 [I,A]; A61K0031-5025 [I,C]; C07D0471-00 [I,C]; C07D0471-00 [I,C]; C07D0471-04 [I,A]; C07D0471-04 [I,A]

IPC RECLASSIF.: A61K0031-502 [I,A]; A61K0031-502 [I,C]; A61K0031-5025 [I,A]; A61K0031-5025 [I,C]; A61K0031-503 [I,A]; A61K0031-503 [I,C]; A61K0031-5375 [I,C]; A61K0031-5377 [I,A]; A61K0031-541 [I,A]; A61K0031-541 [I,C]; A61P0025-00 [I,C]; A61P0025-04 [I,A]; C07D0471-00 [I,C]; C07D0471-04 [I,A]; C07D0487-00 [I,C]; C07D0487-04 [I,A]

## BASIC ABSTRACT:

WO 2001047924 A1 UPAB: 20060117

NOVELTY - Treating a subject suffering from pain involves administering pyridazino quinoline dione compounds (I).

DETAILED DESCRIPTION - Treating a subject suffering from pain involves administering pyridazino quinoline dione compounds of formula (I).

A = (CH<sub>2</sub>)<sub>n</sub>;

n = 0-4;

R<sub>1</sub> = halo;

D-E = group of formula (i);

R<sub>2</sub> = H, OH, halo, 1-4C alkyl, 1-4C alkoxy, hydroxy 2-6C alkynyl, 1-3C alkyl OC(O)O, 1-3C alkyl S(O)<sub>m</sub>, benzimidazolyl, C(O)NR<sub>3</sub>R<sub>4</sub>, NR<sub>3</sub>R<sub>4</sub> or NHC(O)NR<sub>3</sub>R<sub>4</sub>;

m = 0-2;

R<sub>3</sub>, R<sub>4</sub> = H, 1-4C alkyl, 1-4C alkoxy, (CH<sub>2</sub>)<sub>n'</sub>01-4C alkyl, 1-3C alkylfuranyl, cyclohexyl or phenyl; or

NR<sub>3</sub>R<sub>4</sub> = morpholinyl, piperazinyl or pyrrolidinyl; and

n' = 1-4;

provided that at least one of R<sub>2</sub> is not H.

An INDEPENDENT CLAIM is also included for the preparation of (I) involving: (i) reacting ketone/aldehyde ED-C(O)-R with BocNHNH<sub>2</sub> in the presence of tetrahydrofuran or MeOH to give ED-C(NNHBoc)-R (II), where (II) is either hydrogenated using 10%Pd/C at 40 psi for 2-18 hours or reduced to give Boc-protected hydrazine (Boc)N(H)N(H)ADE (III), or EDAX is reacted to give the Boc-protected hydrazine. Alternatively an alternative hydrazine is prepared by reacting an aromatic aldehyde H-C(O)DCO<sub>2</sub>H with NH<sub>2</sub>NNHBoc to give HC(=NNHBoc)DCO<sub>2</sub>H which is further reacted with DPPA, PhMe and R<sub>3</sub>R<sub>4</sub>NH and heated to give HC(=NNHBoc)DNC(O)-NR<sub>3</sub>R<sub>4</sub> (IV). (IV) is reacted with ammonium formate in the presence of 10% Pd/C catalyst to give NNHBoc-C-D-N-C(O)NR<sub>3</sub>R<sub>4</sub>; or ii) coupling (III) with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide or other coupling reagent and cyclizing the product.

ACTIVITY - Analgesic.

MECHANISM OF ACTION - N-methyl-D-aspartate (NMDA) receptor activity inhibitor.

Binding of 7-chloro-4-hydroxy-2-(4-(3-proparginol)phenyl)-1,2,5,10-tetrahydropyridazino(4,5-b)quinoline-1,10-dione (Ib) to the N-methyl-D-aspartate (NMDA) receptor glycine site is assessed by measuring the ability of (Ib) to inhibit the binding of tritiated MDL105, 519 to brain membranes bearing the receptor. The potency (K<sub>i</sub>) of (A) is found to be 1.0 nM.

USE - In prophylactic treatment of pain (claimed) or nociception particularly for the amelioration of neuropathic pain in mammals e.g. humans.

MANUAL CODE: CPI: B06-D17; B14-C01; B14-L06; N02-F01

## TECH

ORGANIC CHEMISTRY - Preparation: (Boc)N(H)N(H)AD is obtained by the hydrogenation of the corresponding imine at 40 psi for 2-18 hours or by hydride mediated reduction. The hydrazine is coupled with 4-hydroxy-2-pyrrolidine carbonyl-quinoline-3-carboxylic acid using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-para-toluenesulfonate or other coupling agent to form a bis amide which was cyclized intermolecularly with methanesulfonic acid as room-temperature in tetrahydrofuran to form (I).

ABEX DEFINITIONS - Preferred Definitions: - n = 1; - R<sub>1</sub> = Cl; - R<sub>2</sub> = H, OH, bromo, iodo, methyl, ethyl, methoxy, ethoxy, hydroxyproparginyl, methylcarboxylate, methylthio, benzimidazole-5-yl, dimethylamino,

NHC(O)NR3R4 or OC(O)NR3R4; - R3, R4 = H, methyl, ethyl, methoxy, (CH2)20-1-2C alkyl, methylfuran-2-yl, cyclohexyl or phenyl.

ADMINISTRATION - The compound can be administered orally, topically, parenterally, buccally, nasally, vaginally or rectally or by inhalation. No dosage given.

SPECIFIC COMPOUNDS - 28 Compounds (I) are specifically claimed e.g. 7-chloro-4-hydroxy-2-((3-(piperazinylcarbonyl)phenyl)methyl)-1,2,5,10-tetrahydropyridazino(4,5-b)quinoline-1,10-dione methanesulfonate (Ia).

EXAMPLE - To a slurry of 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (0.65 g) in dichloromethane (DCM) (40 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.44 g) and stirred for 5 minutes. To the mixture was added a solution of (tert-butoxy)-N-(3-(1-piperazinylcarbonyl)phenyl)methylamino)carboxamide (0.93 g) and 4-(dimethylamino)pyridine (DMAP) (0.02 g) in DCM (10 ml), refluxed for 4 hours, cooled and diluted with DCM (50 ml). The DCM was extracted, dried over MgSO4 and the solvent was removed to give N-((tert-butoxy)carbonylamino)(7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)-N-((3-(1-piperazinylcarbonyl)phenyl)methylcarboxamide (86%). To a solution of this compound (1.3 g) in tetrahydrofuran (THF) (30 ml) was added methanesulfonic acid (4 ml) and stirred overnight. The volatiles were removed and to the residual oil was added diethyl ether (200 ml). The mixture was stirred and then allowed to settle into two layers. To the oil was added water (5 ml), followed by sodium chloride. The precipitate formed was filtered, washed and sonicated in 20 ml of 5/1 diethyl ether/methyl alcohol for 15 minutes. The material was filtered, washed and dried to give 7-chloro-4-hydroxy-2-((3-(piperazinylcarbonyl)phenyl)methyl)-1,2,5,10-tetrahydropyridazino(4,5-b)quinoline-1,10-dione methanesulfonate (44%).

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L99 ANSWER 43 OF 69 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 135:107325 MARPAT Full-text

TITLE: Preparation of pyrazolopyridines as adenosine antagonists and their use for treatment of various diseases

INVENTOR(S): Akabane, Atsushi; Kuroda, Satoshi; Itani, Hiromichi

PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 22 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

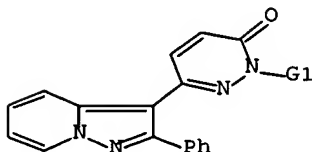
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001192384	A	20010717	JP 2000-378350	20001213
PRIORITY APPLN. INFO.:			AU 1999-4622	19991213

AB Pyrazolopyridines I [R = lower alkenyl- or aryl-substituted lower alkyl (linked by O), AR1; R1 = substituted oxadiazolyl, thiazolyl, oxazolyl, imidazolyl; A = lower alkylene] or their salts are prepared by N-substitution of I (R = H), cyclocondensation of I [R = AC(NH2):NOH; A = same as above] with R2COX2 (R2 = lower alkyl; X2 = leaving group), etc. Thus, 2.88 g I (R = H) was treated with NaH and allyl bromide at room temperature for 2 h in DMF to give

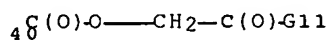
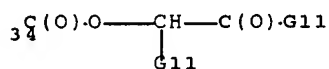
2.04 g I (R = allyl), which inhibited binding of [3H]DPCPX to A1 receptor, and [3H]CGS21680 to A2a receptor with  $K_i$  values of 0.04 and 2.69 nM, resp.

MSTR 1

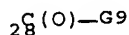
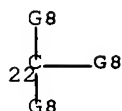
G1 = alkenyl <containing 2-6 C> /  
alkyl <containing 1-6 C> (substd. by 1 or more G2) / 19 /  
(Specifically claimed: CH<sub>2</sub>CH=CH<sub>2</sub>)

<sup>19</sup>G<sup>5</sup>—G<sup>6</sup>

G2 = aryl (opt. substd. by 1 or more G3) /  
alkoxy <containing 1-6 C> (opt. substd. by G4) /  
(Specifically claimed: Ph)  
G3 = R / (Examples: Cl / Br / F / I /  
alkyl <containing 1-6 C> / alkoxy <containing 1-6 C> / OH /  
NO<sub>2</sub>)  
G4 = aryl (opt. substd. by 1 or more G3)  
G5 = alkylene <containing 1-6 C> /  
(Specifically claimed: CH<sub>2</sub>)  
G6 = oxadiazolyl (opt. substd. by 1 or more G7) /  
thiazolyl (opt. substd. by 1 or more G7) /  
oxazolyl (opt. substd. by 1 or more G7) /  
imidazolyl (opt. substd. by 1 or more G7) / 34 / 40 /  
(Specifically claimed: CO<sub>2</sub>H)

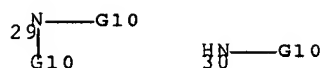


G7 = alkyl <containing 1-6 C> (opt. substd. by CO<sub>2</sub>H) /  
acyl / aryl / pyridyl / 22 / CO<sub>2</sub>H /  
(Specifically claimed: Ph / pyridyl / 28 / CH<sub>2</sub>OH)



G8 = Cl / Br / F / I

G9 = NH2 / 29 / 30 / heterocycle <attached through 1 or more N>



G10 = alkyl <containing 1-6 C>  
(opt. substd. by dialkylamino <each alkyl containing 1-6 C>  
) / aryl (opt. substd. by 1 or more G3)

G11 = alkyl <containing 1-6 C> / Ph

Derivative: or salts

Patent location: claim 1

=> d ibib ed ab ind 44-69

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE, DRUGU, MARPAT' - CONTINUE? (Y)/N:y

L99 ANSWER 44 OF 69 MEDLINE on STN

ACCESSION NUMBER: 1998358188 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9691090

TITLE: Phosphodiesterase 3 inhibitors suppress oocyte maturation and consequent pregnancy without affecting ovulation and cyclicity in rodents.

AUTHOR: Wiersma A; Hirsch B; Tsafiriri A; Hanssen R G; Van de Kant M; Kloosterboer H J; Conti M; Hsueh A J

CORPORATE SOURCE: Department of Pharmacology, N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.. a.wiersma@organon.oss.akzonobel.nl

CONTRACT NUMBER: P50 HD31398 (NICHD)

SOURCE: The Journal of clinical investigation, (1998 Aug 1) Vol. 102, No. 3, pp. 532-7.  
Journal code: 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 3 Sep 1998

Last Updated on STN: 3 Mar 2000

Entered Medline: 26 Aug 1998

ED Entered STN: 3 Sep 1998

Last Updated on STN: 3 Mar 2000

Entered Medline: 26 Aug 1998

AB During each reproductive cycle, a preovulatory surge of gonadotropins induces meiotic maturation of the oocyte in the preovulatory follicle followed by ovulation. Although gonadotropins stimulate cAMP production in somatic cells of the follicle, a decrease in intra-oocyte cAMP levels is required for resumption of meiosis in oocytes. Based on the observed compartmentalization of the cAMP-degrading enzyme, phosphodiesterase, in follicular somatic and germ cells, inhibitors of phosphodiesterase 3 were used to block meiosis in ovulating oocytes in rodents. By this strategy, we demonstrated that fertilization and pregnancy could be prevented without disturbing follicle rupture and normal estrous cyclicity. In contrast to conventional

contraceptive pills that disrupt ovarian steroidogenesis and reproductive cycles, the present strategy achieves effective contraception by selective blockage of oocyte maturation and development without alterations in ovulation and reproductive cyclicity.

CT Check Tags: Female

1-Methyl-3-isobutylxanthine: PD, pharmacology

\*3',5'-Cyclic-Nucleotide Phosphodiesterase: AI, antagonists & inhibitors

Animals

Comparative Study

\*Contraceptive Agents, Female: PD, pharmacology

\*Cyclic AMP: PH, physiology

\*Estrus: DE, drug effects

Fertilization: DE, drug effects

Heart Rate: DE, drug effects

Hypoxanthine: PD, pharmacology

Isoenzymes: AI, antagonists & inhibitors

\*Meiosis: DE, drug effects

Menotropins: PD, pharmacology

Mice

Mice, Inbred C57BL

Milrinone

\*Oogenesis: DE, drug effects

Ovarian Follicle: DE, drug effects

Ovarian Follicle: PH, physiology

\*Ovulation: DE, drug effects

Ovulation Induction

\*Phosphodiesterase Inhibitors: PD, pharmacology

Pregnancy

Purinones: PD, pharmacology

Pyridazines: PD, pharmacology

Pyridones: PD, pharmacology

Pyrrolidinones: PD, pharmacology

Quinolones: PD, pharmacology

Rats

Rats, Sprague-Dawley

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Rolipram

\*Second Messenger Systems: PH, physiology

Substrate Specificity

Thiophenes: PD, pharmacology

RN 129425-83-8 (Org 9935); 28822-58-4 (1-Methyl-3-isobutylxanthine);  
37762-06-4 (zaprinast); 60-92-4 (Cyclic AMP); 61413-54-5 (Rolipram);  
61489-71-2 (Menotropins); 68-94-0 (Hypoxanthine); 68550-75-4  
(cilostamide); 74150-27-9 (pimobendan); 78415-72-2 (Milrinone)

CN 0 (Contraceptive Agents, Female); 0 (Isoenzymes); 0 (  
Phosphodiesterase Inhibitors); 0 (Purinones); 0 (Pyridazines); 0  
(Pyridones); 0 (Pyrrolidinones); 0 (Quinolones); 0 (Thiophenes);  
EC 3.1.4.- (phosphodiesterase III); EC 3.1.4.17  
(3',5'-Cyclic-Nucleotide Phosphodiesterase)

L99 ANSWER 45 OF 69

MEDLINE on STN

ACCESSION NUMBER: 1998365599 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9700242

TITLE: Pharmacologic agents inhibit rat mesangial cell  
proliferation and collagen synthesis.

AUTHOR: Fang C C; Yen C J; Shyu R S; Wu M S; Tsai T J; Hsieh B S

CORPORATE SOURCE: Department of Emergency Medicine, College of Medicine,  
National Taiwan University, Taipei, Taiwan.

SOURCE: Journal of the Formosan Medical Association = Taiwan yi zhi, (1998 Jul) Vol. 97, No. 7, pp. 458-64.  
Journal code: 9214933. ISSN: 0929-6646.

PUB. COUNTRY: TAIWAN: Taiwan, Province of China

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 3 Sep 1998  
Last Updated on STN: 3 Sep 1998  
Entered Medline: 27 Aug 1998

ED Entered STN: 3 Sep 1998

Last Updated on STN: 3 Sep 1998

Entered Medline: 27 Aug 1998

AB Prevention of the development of end-stage renal disease is one of the most promising areas of research in nephrology. Because mesangial cell proliferation and extracellular matrix accumulation have been regarded as antecedents of glomerulosclerosis, agents that can inhibit mesangial cell proliferation may have a potential to retard the progression of renal diseases. Therefore, we investigated several clinically available agents that might affect mesangial cell proliferation and collagen synthesis in male Sprague-Dawley rats. Cell proliferation was measured by the tetrazolium dye uptake method. Collagen synthesis was measured by <sup>3</sup>H-proline incorporation into pepsin-resistant, salt-precipitated collagen. Intracellular cAMP levels were measured by enzyme immunoassay. Our results showed that hydralazine (82% inhibition at 10 micrograms/mL), ticlopidine (61% inhibition at 30 micrograms/mL), aminophylline (66% inhibition at 200 micrograms/mL), and nicametate (91% inhibition at 1 mg/mL) inhibited serum-stimulated rat mesangial cell (RMC) growth in a dose-dependent manner. Ticlopidine (43% inhibition at 30 mg/mL), aminophylline (52% inhibition at 200 mg/mL), and nicametate (35% inhibition at 1 mg/mL) inhibited collagen synthesis in confluent RMCs. Aminophylline may act through increasing intracellular cAMP levels (9.7 +/- 0.7 pmol/mg protein at 200 micrograms/mL of aminophylline vs 4.2 +/- 0.6 pmol/mg protein at control). These data suggest that aminophylline, ticlopidine, hydralazine, and nicametate can inhibit RMC proliferation and collagen synthesis.

CT Check Tags: Male

Aminophylline: PD, pharmacology

Analysis of Variance

Animals

\*Cardiovascular Agents: PD, pharmacology

\*Collagen: BI, biosynthesis

\*Collagen: DE, drug effects

\*Glomerular Mesangium: CY, cytology

\*Glomerular Mesangium: DE, drug effects

Hydralazine: PD, pharmacology

Nicotinic Acids: PD, pharmacology

Rats

Rats, Sprague-Dawley

Research Support, Non-U.S. Gov't

Ticlopidine: PD, pharmacology

RN 1641-74-3 (nicametate); 317-34-0 (Aminophylline); 55142-85-3 (Ticlopidine); 86-54-4 (Hydralazine); 9007-34-5 (Collagen)

CN 0 (Cardiovascular Agents); 0 (Nicotinic Acids)

L99 ANSWER 46 OF 69 MEDLINE on STN

ACCESSION NUMBER: 96031070 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 8564209

TITLE: Effects of type-selective phosphodiesterase inhibitors on glucose-induced insulin secretion and islet

phosphodiesterase activity.  
 AUTHOR: Shafiee-Nick R; Pyne N J; Furman B L  
 CORPORATE SOURCE: Department of Physiology and Pharmacology, University of Strathclyde, Glasgow.  
 SOURCE: British journal of pharmacology, (1995 Aug) Vol. 115, No. 8, pp. 1486-92.  
 Journal code: 7502536. ISSN: 0007-1188.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199603  
 ENTRY DATE: Entered STN: 15 Mar 1996  
 Last Updated on STN: 3 Mar 2000  
 Entered Medline: 4 Mar 1996

ED Entered STN: 15 Mar 1996  
 Last Updated on STN: 3 Mar 2000  
 Entered Medline: 4 Mar 1996

AB 1. We examined various type-selective phosphodiesterase (PDE) inhibitors on glucose-induced insulin secretion from rat isolated islets, on islet PDE activity and on islet cyclic AMP accumulation in order to assess the relationship between type-selective PDE inhibition and modification of insulin release. 2. The non-selective PDE inhibitor, 3-isobutyl-1-methylxanthine (IBMX, 10(-5)-10(-3) M), as well as the type III selective PDE inhibitors SK&F 94836 (10(-5)-10(-3) M), Org 9935 (10(-7)-10(-4) M), SK&F 94120 (10(-5)-10(-4) M) and ICI 118233 (10(-6)-10(-4) M) each caused concentration-dependent augmentation (up to 40% increase) of insulin release in the presence of a stimulatory glucose concentration (10 mM), but not in the presence of 3 mM glucose. 3. Neither the type IV PDE inhibitor rolipram (10(-4) M) nor the type I and type V PDE inhibitor, zaprinast (10(-4)-10(-3) M) modified glucose-induced insulin release when incubated with islets, although a higher concentration of rolipram (10(-3) M) inhibited secretion by 55%. However, when islets were preincubated with these drugs followed by incubation in their continued presence, zaprinast (10(-6)-10(-4) M) produced a concentration-dependent inhibition (up to 45% at 10(-4) M). Under these conditions, rolipram inhibited insulin secretion at a lower concentration (10(-4) M) than when simply incubated with islets. 4. A combination of SK&F 94836 (10(-5) M) and forskolin (5 x 10(-8) M) significantly augmented glucose-induced insulin secretion (30% increase), although neither drug alone, in these concentrations, produced any significant effect. (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Male

1-Methyl-3-isobutylxanthine: PD, pharmacology

3',5'-Cyclic-Nucleotide Phosphodiesterase: AI, antagonists & inhibitors

Analysis of Variance

Animals

Cyclic AMP: ME, metabolism

Dose-Response Relationship, Drug

Drug Interactions

Forskolin: PD, pharmacology

\*Glucose: PD, pharmacology

Guanidines: PD, pharmacology

\*Insulin: SE, secretion

\*Islets of Langerhans: DE, drug effects

Islets of Langerhans: ME, metabolism

\*Isoenzymes: ME, metabolism

\*Phosphodiesterase Inhibitors: PD, pharmacology

\*Phosphoric Diester Hydrolases: ME, metabolism

Purinones: PD, pharmacology

Pyrazines: PD, pharmacology

Pyridazines: PD, pharmacology

Pyrrolidinones: PD, pharmacology

Rats

Rats, Sprague-Dawley

Rolipram

Thiophenes: PD, pharmacology

RN 11061-68-0 (Insulin); 115344-47-3 (siguazodan); 129425-83-8 (Org 9935);  
28822-58-4 (1-Methyl-3-isobutylxanthine); 37762-06-4 (zaprinast); 50-99-7  
(Glucose); 60-92-4 (Cyclic AMP); 61413-54-5 (Rolipram); 66428-89-5  
(Forskolin); 89541-55-9 (5-(4-acetamidophenyl)pyrazin-2(1H)-one);  
93851-00-4 (ICI 118233)

CN 0 (Guanidines); 0 (Isoenzymes); 0 (Phosphodiesterase  
Inhibitors); 0 (Purinones); 0 (Pyrazines); 0 (Pyridazines); 0  
(Pyrrolidinones); 0 (Thiophenes); EC 3.1.4 (Phosphoric Diester  
Hydrolases); EC 3.1.4.17 (3',5'-Cyclic-Nucleotide  
Phosphodiesterase)

L99 ANSWER 47 OF 69 MEDLINE on STN

ACCESSION NUMBER: 94361704 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 7521642

TITLE: Synergistic interactions between selective pharmacological  
inhibitors of phosphodiesterase isozyme families  
PDE III and PDE IV to attenuate proliferation of rat  
vascular smooth muscle cells.

AUTHOR: Pan X; Arauz E; Krzanowski J J; Fitzpatrick D F; Polson J B

CORPORATE SOURCE: Department of Pharmacology and Therapeutics, College of  
Medicine, University of South Florida, Tampa 33612-4799.

SOURCE: Biochemical pharmacology, (1994 Aug 17) Vol. 48, No. 4, pp.  
827-35.

Journal code: 0101032. ISSN: 0006-2952.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199409

ENTRY DATE: Entered STN: 13 Oct 1994

Last Updated on STN: 3 Mar 2000

Entered Medline: 30 Sep 1994

ED Entered STN: 13 Oct 1994

Last Updated on STN: 3 Mar 2000

Entered Medline: 30 Sep 1994

AB The interaction between selective inhibitors of 3',5'-cyclic-nucleotide  
phosphodiesterase (PDE) III (cyclic GMP inhibited phosphodiesterase) and  
selective inhibitors of PDE IV (Ro 20-1724 inhibited phosphodiesterase) to  
attenuate fetal bovine serum-stimulated incorporation of [3H]thymidine into  
DNA and cell proliferation was studied in a line (A10) of vascular smooth  
muscle cells (VSMC). The nonselective PDE inhibitors 3-isobutyl-1-  
methylxanthine (IBMX) and papaverine attenuated DNA synthesis with EC50 values  
(16 and 18 microM, respectively) in the same range as their published IC50  
values (2-50 and 2-25 microM, respectively) as PDE inhibitors. The selective  
PDE III inhibitors CI-930 and cilostamide used alone attenuated DNA synthesis  
with EC50 values (> 300 and 5.3 microM, respectively) that were much higher  
than published IC50 values (0.15-0.46 and 0.005-0.064 microM, respectively)  
for inhibition of PDE III. In the presence of the PDE IV inhibitor rolipram  
(10 microM), their EC50 values were shifted (0.66 and 0.16 microM,  
respectively) much closer to their respective IC50 values. When the selective  
PDE IV inhibitors rolipram and Ro 20-1724 were used alone, they attenuated DNA  
synthesis with EC50 values (111 and > 100 microM, respectively) much higher  
than their IC50 values (0.6-2.6 and 2-13 microM, respectively) as inhibitors

of PDE IV, but 10 microM CI-930 (PDE III inhibitor) shifted their EC50 values (0.56 and 1.5 microM, respectively) much closer to their IC50 values. In experiments that assessed VSMC proliferation using the MTT [3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] method, IBMX and papaverine attenuated proliferation with EC50 values (27 and 58 microM, respectively) close to their IC50 values. CI-930 and cilostamide used alone did not cause 50% attenuation of proliferation at the highest concentrations tested (100 and 10 microM, respectively). In the presence of 5 microM rolipram, however, their effects were enhanced greatly with EC50 values (0.86 and 0.23 microM, respectively) that were close to their IC50 values as PDE III inhibitors. Similarly, rolipram and Ro 20-1724 attenuated VSMC proliferation with EC50 values close to their IC50 values in the presence (2.1 and 4.6 microM, respectively) but not in the absence (> 100 and > 10 microM, respectively) of 2 microM CI-930. The interactions between PDE III inhibitors and PDE IV inhibitors to attenuate DNA synthesis and VSMC proliferation were synergistic as determined by the combination index. The data demonstrate that the synergistic interactions that attenuate incorporation of [3H]thymidine into DNA are accompanied by synergistic attenuations of VSMC division. (ABSTRACT TRUNCATED AT 400 WORDS)

CT 1-Methyl-3-isobutylxanthine: PD, pharmacology

Animals

Cell Division: DE, drug effects

Cell Line

Comparative Study

Drug Synergism

Isoenzymes: AI, antagonists & inhibitors

Models, Chemical

\*Muscle, Smooth, Vascular: EN, enzymology

\*Phosphodiesterase Inhibitors: PD, pharmacology

\*Phosphoric Diester Hydrolases: ME, metabolism

Pyridazines: PD, pharmacology

Pyrrolidinones: PD, pharmacology

Quinolones: PD, pharmacology

Rats

Research Support, Non-U.S. Gov't

Rolipram

Thymidine: ME, metabolism

RN 28822-58-4 (1-Methyl-3-isobutylxanthine); 50-89-5 (Thymidine); 61413-54-5 (Rolipram); 68550-75-4 (cilostamide); 86798-59-6 (4,5-dihydro-6-(4-(imidazol-1-yl)phenyl)-5-methyl-3(2H)-pyridazinone)

CN 0 (Isoenzymes); 0 (Phosphodiesterase Inhibitors); 0 (Pyridazines); 0 (Pyrrolidinones); 0 (Quinolones); EC 3.1.4 (Phosphoric Diester Hydrolases)

L99 ANSWER 48 OF 69

MEDLINE on STN

ACCESSION NUMBER: 91115456 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 1703513

TITLE: A method for evaluating anti-allergic drugs by simultaneously induced passive cutaneous anaphylaxis and mediator cutaneous reactions.

AUTHOR: Koda A; Miura T; Inagaki N; Sakamoto O; Arimura A; Nagai H; Mori H

CORPORATE SOURCE: Department of Pharmacology, Gifu Pharmaceutical University, Japan.

SOURCE: International archives of allergy and applied immunology, (1990) Vol. 92, No. 3, pp. 209-16.

Journal code: 0404561. ISSN: 0020-5915.

PUB. COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199103  
ENTRY DATE: Entered STN: 29 Mar 1991  
Last Updated on STN: 29 Jan 1996  
Entered Medline: 6 Mar 1991

ED Entered STN: 29 Mar 1991  
Last Updated on STN: 29 Jan 1996  
Entered Medline: 6 Mar 1991

AB Homologous passive cutaneous anaphylaxis (PCA) was induced by IgE antibody and, simultaneously, cutaneous reactions were induced by some allergic mediators such as histamine, serotonin and leukotriene (LT) C4 on rat back skin. Disodium cromoglycate and tranilast with inhibitory actions on mediator release inhibited PCA specifically, whereas antihistaminics, including ketotifen, azelastine, mequitazine and diphenhydramine, inhibited histamine- and serotonin-induced cutaneous reactions as well as PCA. Anti-slow-reacting substance of anaphylaxis drugs, KC-404 and FPL-55712, significantly inhibited PCA and histamine- and serotonin-induced reactions, but at the same doses they did not produce significant inhibition of the LTC4-induced reaction. All reactions tested were strongly inhibited dose dependently with the beta stimulants, salbutamol and isoproterenol, and a xanthine derivative, theophylline, which are known to increase the intracellular cyclic AMP level. We think that this method enables the determination of the properties of anti-allergic drugs.

CT Check Tags: Female; Male  
Albuterol: PD, pharmacology  
Animals  
Anthranilic Acids: PD, pharmacology  
Diphenhydramine: PD, pharmacology  
Dose-Response Relationship, Drug  
\*Histamine H1 Antagonists: PD, pharmacology  
Isoproterenol: PD, pharmacology  
Ketotifen: PD, pharmacology  
\*Passive Cutaneous Anaphylaxis: DE, drug effects  
Phenothiazines: PD, pharmacology  
Phthalazines: PD, pharmacology  
Rats  
Rats, Inbred Strains  
Skin Tests  
Theophylline: PD, pharmacology

RN 18559-94-9 (Albuterol); 29216-28-2 (mequitazine); 34580-13-7 (Ketotifen); 53902-12-8 (tranilast); 58-55-9 (Theophylline); 58-73-1 (Diphenhydramine); 58581-89-8 (azelastine); 7683-59-2 (Isoproterenol)

CN 0 (Anthranilic Acids); 0 (Histamine H1 Antagonists); 0 (Phenothiazines); 0 (Phthalazines)

L99 ANSWER 49 OF 69 MEDLINE on STN  
ACCESSION NUMBER: 90119968 MEDLINE Full-text  
DOCUMENT NUMBER: PubMed ID: 2575358  
TITLE: Inhibitory effect of adenine nucleotides and anti-allergic drugs on phosphorylation of phosphatidylinositol in rat mast cell granules.  
AUTHOR: Kurosawa M; Okayama Y; Kobayashi S  
CORPORATE SOURCE: First Department of Internal Medicine, Gunma University School of Medicine, Japan.  
SOURCE: Allergy, (1989 Nov) Vol. 44, No. 8, pp. 576-81.  
Journal code: 7804028. ISSN: 0105-4538.  
PUB. COUNTRY: Denmark  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199002  
 ENTRY DATE: Entered STN: 28 Mar 1990  
 Last Updated on STN: 6 Feb 1998  
 Entered Medline: 12 Feb 1990

ED Entered STN: 28 Mar 1990  
 Last Updated on STN: 6 Feb 1998  
 Entered Medline: 12 Feb 1990

AB Rat mast cell granules were obtained by sonication of highly purified rat mast cells and isolated in a Percoll gradient. Phosphorylation of endogenous phosphatidylinositol in rat mast cell granules, which is catalyzed by phosphatidylinositol kinase in the granules, was assayed by measuring the incorporation of <sup>32</sup>P from [gamma <sup>32</sup>P]ATP into phosphatidylinositol 4-phosphate. Lipids were isolated with methanol/chloroform/HCl and were separated by thin-layer chromatography on oxalic acid impregnated silica gel plates. Phosphatidylinositol 4-phosphate areas were identified by staining with iodine, scraped and measured for <sup>32</sup>P radioactivity. The phosphorylation reaction was inhibited by 50-500 microm adenosine, ADP and 500 microm AMP in a concentration-dependent manner. Among several anti-allergic drugs investigated. 100-1000 microm theophylline and 10-100 microm azelastine inhibited the phosphorylation reaction, but disodium cromoglycate and ketotifen had little effect.

CT 1-Phosphatidylinositol 4-Kinase  
 \*Adenine Nucleotides: PD, pharmacology  
 Adenosine: PD, pharmacology  
 Adenosine Diphosphate: PD, pharmacology  
 Adenosine Monophosphate: PD, pharmacology  
 Animals  
 Cromolyn Sodium: PD, pharmacology  
 \*Cytoplasmic Granules: ME, metabolism  
 Histamine H1 Antagonists: PD, pharmacology  
Ketotifen: PD, pharmacology  
 \*Mast Cells: ME, metabolism  
 Mast Cells: UL, ultrastructure  
 \*Phosphatidylinositols: ME, metabolism  
 Phosphorylation  
 Phosphotransferases: AI, antagonists & inhibitors  
Phthalazines: PD, pharmacology  
 Rats  
Theophylline: PD, pharmacology

RN 15826-37-6 (Cromolyn Sodium); 34580-13-7 (Ketotifen); 58-55-9 (Theophylline); 58-61-7 (Adenosine); 58-64-0 (Adenosine Diphosphate); 58581-89-8 (azelastine); 61-19-8 (Adenosine Monophosphate)  
 CN 0 (Adenine Nucleotides); 0 (Histamine H1 Antagonists); 0 (Phosphatidylinositols); 0 (Phthalazines); EC 2.7 (Phosphotransferases); EC 2.7.1.67 (1-Phosphatidylinositol 4-Kinase)

L99 ANSWER 50 OF 69 MEDLINE on STN  
 ACCESSION NUMBER: 89390254 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 2571246  
 TITLE: The effect of azelastine and some other antiasthmatic and antiallergic drugs on calmodulin and protein kinase C.  
 AUTHOR: Middleton E Jr; Ferriola P; Drzewiecki G; Sofia R D  
 CORPORATE SOURCE: Department of Medicine State University of New York, Buffalo 14214.  
 SOURCE: Agents and actions, (1989 Aug) Vol. 28, No. 1-2, pp. 9-15. Journal code: 0213341. ISSN: 0065-4299.  
 PUB. COUNTRY: Switzerland  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals

ENTRY MONTH: 198910  
 ENTRY DATE: Entered STN: 9 Mar 1990  
 Last Updated on STN: 6 Feb 1995  
 Entered Medline: 26 Oct 1989

ED Entered STN: 9 Mar 1990  
 Last Updated on STN: 6 Feb 1995  
 Entered Medline: 26 Oct 1989

AB The antiallergic and antiasthmatic drug, azelastine, interacts strongly with calmodulin (but not bovine serum albumin) as determined by an indirect assay; it also moderately inhibited the Ca<sup>2+</sup>-calmodulin-dependent enzyme bovine brain phosphodiesterase. Ketotifen was less active than azelastine in both assays of calmodulin reactivity and both drugs were less active than the recognized calmodulin inhibitor, W-7. Neither azelastine nor ketotifen had any inhibitory effect on the Ca<sup>2+</sup>- and phospholipid-dependent protein kinase C. A number of other commonly employed antiallergic and antiasthmatic drugs were essentially inactive in the calmodulin assays and had no or marginal inhibitory effect on protein kinase C.

CT 3',5'-Cyclic-Nucleotide Phosphodiesterase: AI, antagonists & inhibitors

Animals

Brain: EN, enzymology

Calcium: PD, pharmacology

\*Calmodulin: AI, antagonists & inhibitors

Calmodulin: PD, pharmacology

Comparative Study

Fluorescent Dyes

\*Histamine H1 Antagonists: PD, pharmacology

Ketotifen: PD, pharmacology

Phosphodiesterase Inhibitors

\*Phthalazines: PD, pharmacology

\*Protein Kinase C: AI, antagonists & inhibitors

\*Pyridazines: PD, pharmacology

Rats

Serum Albumin, Bovine: ME, metabolism

Spectrometry, Fluorescence

Sulfonamides: PD, pharmacology

RN 34580-13-7 (Ketotifen); 58581-89-8 (azelastine); 65595-90-6 (W 7);  
 7440-70-2 (Calcium)

CN 0 (Calmodulin); 0 (Fluorescent Dyes); 0 (Histamine H1 Antagonists); 0 ( Phosphodiesterase Inhibitors); 0 (Phthalazines); 0 (Pyridazines);  
 0 (Serum Albumin, Bovine); 0 (Sulfonamides); EC 2.7.1.37 (Protein Kinase C); EC 3.1.4.17 (3',5'-Cyclic-Nucleotide Phosphodiesterase)

L99 ANSWER 51 OF 69

MEDLINE on STN

ACCESSION NUMBER: 89157873 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 2466139

TITLE: Therapeutic aspects of intractable asthma.

AUTHOR: Tomioka S; Kuroiwa H

SOURCE: Nihon Ky bu Shikkan Gakkai zasshi, (1988 Mar) Vol. 26, No. 3, pp. 242-7.

Journal code: 7505737. ISSN: 0301-1542.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198904

ENTRY DATE: Entered STN: 6 Mar 1990

Last Updated on STN: 29 Jan 1999

Entered Medline: 13 Apr 1989

ED Entered STN: 6 Mar 1990

Last Updated on STN: 29 Jan 1999

Entered Medline: 13 Apr 1989

CT Check Tags: Female; Male

Adult

Aged

Anthranilic Acids: PK, pharmacokinetics

Anthranilic Acids: TU, therapeutic use

\*Asthma: DT, drug therapy

Cromolyn Sodium: PK, pharmacokinetics

Cromolyn Sodium: TU, therapeutic use

English Abstract

Humans

Ketotifen: TU, therapeutic use

Middle Aged

Phthalazines: TU, therapeutic use

Terbutaline: AA, analogs &amp; derivatives

Terbutaline: PK, pharmacokinetics

Theophylline: PK, pharmacokinetics

RN 15826-37-6 (Cromolyn Sodium); 23031-25-6 (Terbutaline); 34580-13-7  
(Ketotifen); 41570-61-0 (tulobuterol); 53902-12-8 (tranilast); 58-55-9  
(Theophylline); 58581-89-8 (azelastine)

CN 0 (Anthranilic Acids); 0 (Phthalazines)

L99 ANSWER 52 OF 69 MEDLINE on STN

ACCESSION NUMBER: 85260072 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 2410374

TITLE: Inhibition of allergic histamine release by azelastine and selected antiallergic drugs from rabbit leukocytes.

AUTHOR: Chand N; Pillar J; Diamantis W; Sofia R D

SOURCE: International archives of allergy and applied immunology,  
(1985) Vol. 77, No. 4, pp. 451-5.  
Journal code: 0404561. ISSN: 0020-5915.

PUB. COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198509

ENTRY DATE: Entered STN: 20 Mar 1990

Last Updated on STN: 6 Feb 1995

Entered Medline: 16 Sep 1985

ED Entered STN: 20 Mar 1990

Last Updated on STN: 6 Feb 1995

Entered Medline: 16 Sep 1985

AB The ability of azelastine to inhibit allergic histamine release from rabbit mixed leukocytes was studied and compared with selected antiallergic drugs. Azelastine, ketotifen, diphenhydramine, theophylline and disodium cromoglycate (DSCG) produced concentration-dependent inhibition of allergic histamine release from rabbit basophils. The concentrations inhibiting histamine release by 50% (IC<sub>50</sub>; microM) were as follows: azelastine = 4.5; ketotifen = 9.5; diphenhydramine = 18.9; theophylline = 56.9; DSCG = greater than 1,000. DSCG was added to the cells immediately prior to antigen challenge. All other drugs were preincubated for a period of 10 min prior to antigen challenge. At the IC<sub>50</sub> level, azelastine is about 2, 4, 13 and greater than 200 times as effective as ketotifen, diphenhydramine, theophylline and DSCG, respectively. The IC<sub>50</sub> of azelastine following 0, 10 and 30 min preincubation were 2.4, 1.9 and 3.5 microM, respectively. These observations showed: (1) azelastine is capable of acting rapidly on basophils and of inhibiting allergic histamine secretion, and (2) the prolongation of the preincubation time of azelastine up to 30 min with rabbit leukocytes did not exhibit any sign of tachyphylaxis (loss of activity). In conclusion, azelastine is a potent inhibitor of

allergic histamine secretion from the leukocytes of ragweed-sensitized rabbits.

CT Check Tags: Male

Animals

Comparative Study

Cromolyn Sodium: PD, pharmacology

Diphenhydramine: PD, pharmacology

\*Histamine H1 Antagonists: PD, pharmacology

\*Histamine Release: DE, drug effects

In Vitro

Ketotifen: PD, pharmacology

\*Leukocytes: DE, drug effects

Leukocytes: IM, immunology

\*Phthalazines: PD, pharmacology

\*Pyridazines: PD, pharmacology

Rabbits

Theophylline: PD, pharmacology

Time Factors

RN 15826-37-6 (Cromolyn Sodium); 34580-13-7 (Ketotifen); 58-55-9

(Theophylline); 58-73-1 (Diphenhydramine); 58581-89-8 (azelastine)

CN 0 (Histamine H1 Antagonists); 0 (Phthalazines); 0 (Pyridazines)

L99 ANSWER 53 OF 69 MEDLINE on STN

ACCESSION NUMBER: 86022470 . MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 2413739

TITLE: Inhibition of IgE-mediated allergic histamine release from rat peritoneal mast cells by azelastine and selected antiallergic drugs.

AUTHOR: Chand N; Pillar J; Diamantis W; Sofia R D

SOURCE: Agents and actions, (1985 Jul) Vol. 16, No. 5, pp. 318-22.  
Journal code: 0213341. ISSN: 0065-4299.

PUB. COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198511

ENTRY DATE: Entered STN: 21 Mar 1990

Last Updated on STN: 21 Mar 1990

Entered Medline: 18 Nov 1985

ED Entered STN: 21 Mar 1990

Last Updated on STN: 21 Mar 1990

Entered Medline: 18 Nov 1985

AB The ability of azelastine to inhibit IgE-mediated allergic histamine release from the peritoneal mast cells of actively sensitized rats was investigated and compared with selected antiallergic agents. Azelastine added simultaneously with the allergic stimuli (ovalbumin, OA, 10 micrograms/ml + phosphatidylserine, PS, 10 micrograms/ml) or preincubated with cells for 10 min prior to antigen challenge produced similar concentration-dependent inhibition of allergic histamine release. The IC50s (microM) following 10-min preincubation were as follows: azelastine = 4.8; astemizole = 86.3; ketotifen = 112.2; diphenhydramine = 133 and theophylline = 2040.3. At IC50 level azelastine was about 18, 23, 28 and 425 times as effective as astemizole, ketotifen (newer histamine H1-receptor antagonists), diphenhydramine (a traditional H1-receptor antagonist), and theophylline (a phosphodiesterase inhibitor), respectively. Sodium cromoglycate in a concentration range or 1-1000 microM (0 or 10-min preincubation) failed to exert any inhibitory effect. These data showed that among six drugs tested azelastine is the most potent inhibitor of allergic histamine release from rat peritoneal mast cells.

CT Check Tags: Male

Animals

Astemizole  
 Benzimidazoles: PD, pharmacology  
 Comparative Study  
 Diphenhydramine: PD, pharmacology  
 \*Histamine Release: DE, drug effects  
 Hypersensitivity: IM, immunology  
 \*Hypersensitivity: PP, physiopathology  
 \*Immunoglobulin E: PH, physiology

Ketotifen: PD, pharmacology

\*Mast Cells: SE, secretion  
 Ovalbumin: IM, immunology  
 Phosphatidylserines: IM, immunology  
 \*Phthalazines: PD, pharmacology  
 \*Pyridazines: PD, pharmacology

Rats

Rats, Inbred Strains

Theophylline: PD, pharmacology

RN 34580-13-7 (Ketotifen); 37341-29-0 (Immunoglobulin E); 58-55-9  
 (Theophylline); 58-73-1 (Diphenhydramine); 58581-89-8 (azelastine);  
 68844-77-9 (Astemizole); 9006-59-1 (Ovalbumin)  
 CN 0 (Benzimidazoles); 0 (Phosphatidylserines); 0 (Phthalazines); 0  
 (Pyridazines)

L99 ANSWER 54 OF 69 MEDLINE on STN

ACCESSION NUMBER: 85052505 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 6094309

TITLE: Adverse drug reactions in the elderly: case studies.

AUTHOR: Clark B G; Vestal R E

SOURCE: Geriatrics, (1984 Dec) Vol. 39, No. 12, pp. 53-4, 60-3, 66.  
 Journal code: 2985102R. ISSN: 0016-867X.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198501

ENTRY DATE: Entered STN: 20 Mar 1990

Last Updated on STN: 20 Mar 1990

Entered Medline: 14 Jan 1985

ED Entered STN: 20 Mar 1990

Last Updated on STN: 20 Mar 1990

Entered Medline: 14 Jan 1985

AB ADRs in the elderly may present in an atypical manner. Atypical reactions are uncommon and usually cannot be anticipated from the chemical or pharmacologic properties of the drug. In many cases, you may find a careful and thorough drug history and knowledge of drug-related reactions more helpful than an array of laboratory data.

CT Check Tags: Female; Male

Acetazolamide: AE, adverse effects

\*Aged

Anemia, Hemolytic: CI, chemically induced

Bromocriptine: AE, adverse effects

Captopril: AE, adverse effects

Chlorpropamide: AE, adverse effects

Cimetidine: AE, adverse effects

Clonidine: AE, adverse effects

Dienestrol: AE, adverse effects

\*Drug Therapy: AE, adverse effects

Humans

Hydralazine: AE, adverse effects

Lung Diseases: CI, chemically induced

Middle Aged

Nitrofurantoin: AE, adverse effects

Pancreatitis: CI, chemically induced

Papaverine: AE, adverse effects

Peripheral Nervous System Diseases: CI, chemically induced

Procainamide: AE, adverse effects

Propranolol: AE, adverse effects

Sulindac: AE, adverse effects

Theophylline: AE, adverse effects

Timolol: AE, adverse effects

RN 25614-03-3 (Bromocriptine); 26839-75-8 (Timolol); 38194-50-2 (Sulindac);  
4205-90-7 (Clonidine); 51-06-9 (Procainamide); 51481-61-9 (Cimetidine);  
525-66-6 (Propranolol); 58-55-9 (Theophylline); 58-74-2 (Papaverine);  
59-66-5 (Acetazolamide); 62571-86-2 (Captopril); 67-20-9 (Nitrofurantoin);  
84-17-3 (Dienestrol); 86-54-4 (Hydralazine); 94-20-2 (Chlorpropamide)

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ACCESSION NUMBER: 2006040376 EMBASE Full-text

TITLE: Synthesis of original trifluoromethylated 6-aryl-  
pyridazines fused with thiazolidine or  
1,2,4-triazole.

AUTHOR: Brule C.; Bouillon J.-P.; Nicolai E.; Portella C.

CORPORATE SOURCE: C. Portella, Laboratoire Reactions Selectives et  
Applications' Associe au CNRS (UMR 6519), Universite de  
Reims Champagne-Ardenne, Faculte des Sciences, B.P. 1039,  
51687 Reims Cedex 2, France. charles.portella@univ-reims.fr

SOURCE: Synthesis, (5 Jan 2006) No. 1, pp. 103-106. .

Refs: 14

ISSN: 0039-7881 CODEN: SYNTBF

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 9 Feb 2006

Last Updated on STN: 9 Feb 2006

ED Entered STN: 9 Feb 2006

Last Updated on STN: 9 Feb 2006

AB An efficient synthesis of original 8-trifluoromethyl-7H-thiazolo [3,2-b]-and  
1,2,4-triazolo[4,3-b]pyridazines is described. Starting from the 4-  
trifluoromethyl-4,5-dihydropyridazin-3-one, the methodology involves a five-  
membered ring closure, based on the reaction of a bis(electrophilic) reagent  
with an exocyclic heteroatom linked to position 3 and the endocyclic nitrogen  
at position 2 of the pyridazine nucleus. .COPYRGT. Georg Thieme Verlag  
Stuttgart.

CT Medical Descriptors:

\*drug synthesis

\*pharmacophore

substitution reaction

reduction

stereochemistry

amidation

ring closing metathesis

oxidation

infrared spectroscopy

proton nuclear magnetic resonance

carbon nuclear magnetic resonance

mass spectrometry

article

Drug Descriptors:

\*pyridazine derivative: AN, drug analysis\*pyridazine derivative: DV, drug development\*thiazolidine derivative: AN, drug analysis\*thiazolidine derivative: DV, drug development

\*1,2,4 triazole derivative: AN, drug analysis

\*1,2,4 triazole derivative: DV, drug development

\*8 trifluoromethyl 7h thiazolo[3,2 b]pyridazine: AN, drug analysis\*8 trifluoromethyl 7h thiazolo[3,2 b]pyridazine: DV, drugdevelopment

\*8 trifluoromethyl 1,2,4 triazolo[4,3 b]pyridazine: AN, drug analysis

\*8 trifluoromethyl 1,2,4 triazolo[4,3 b]pyridazine: DV, drug development

\*fluorinated hydrocarbon: AN, drug analysis

\*fluorinated hydrocarbon: DV, drug development

4 trifluoromethyl 4,5 dihydropyridazin 3 one

pyridazinone derivative

heterocyclic nitro compound

6 (4' bromophenyl) 8 trifluoromethyl 7h thiazolo[3,2 d]pyridazin 3one: AN, drug analysis6 (4' bromophenyl) 8 trifluoromethyl 7h thiazolo[3,2 d]pyridazin 3one: DV, drug development6 (4' bromophenyl) 3 methyl 8 trifluoromethyl 1,2,4 triazolo[4,3  
b]pyridazine : AN, drug analysis6 (4' bromophenyl) 3 methyl 8 trifluoromethyl 1,2,4 triazolo[4,3  
b]pyridazine : DV, drug development6 (4' bromophenyl) 8 trifluoromethyl 1,2,4 triazolo[4,3 b]pyridazin 3 one:  
AN, drug analysis6 (4' bromophenyl) 8 trifluoromethyl 1,2,4 triazolo[4,3 b]pyridazin 3 one:  
DV, drug development3 amino 6 (4' bromophenyl) 8 trifluoromethyl 1,2,4 triazolo[4,3  
b]pyridazine : AN, drug analysis3 amino 6 (4' bromophenyl) 8 trifluoromethyl 1,2,4 triazolo[4,3  
b]pyridazine : DV, drug development

unclassified drug

L99 ANSWER 56 OF 69 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights  
reserved on STNACCESSION NUMBER: 2006038115 EMBASE Full-textTITLE: Facile route for the synthesis of pyridazine  
derivatives: Unexpected pathway to benzothiazole,  
benzimidazole, and triazole derivatives.

AUTHOR: El Rady E.A.

CORPORATE SOURCE: E.A. El Rady, Chemistry Department, Faculty of Science,  
South Valley University, Aswan, Egypt.  
emanelradi@hotmail.comSOURCE: Synthetic Communications, (1 Feb 2006) Vol. 36, No. 1, pp.  
37-49. .

Refs: 11

ISSN: 0039-7911 CODEN: SYNCAV

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 9 Feb 2006

Last Updated on STN: 9 Feb 2006

ED Entered STN: 9 Feb 2006

Last Updated on STN: 9 Feb 2006

AB 4-Amino-5-arylmethylidene-3-phenyl-pyridazin-6-ones 7 have been synthesized and reacted with selected nucleophile reagents such as phenyl hydrazine, semicarbazide, semithiocarbazide, cyanoacetohydrazide, 2- aminothiophenol, and 2-phenylenediamine in ethanol triethyl-amine solution. An unexpected 1-phenyl-3-arylaziridine 10, 3-aryl-5-oxo(thio)- 1,2,4-triazole 21, 4-amino-3-aryl-6-hydroxy-pyridazine 27, 2- arylbenzothiazole 30a-c, and 2-arylbenzimidazole 30d-f have been obtained, respectively. Also, 2- aminothiophenol and 2-phenylenediamine were reacted with N-phenylmethylidene-2-cyanoacetohydrazide 2, affording the new 1,4-benzodiazepine derivatives 35. Copyright .COPYRGT. Taylor & Francis LLC.

CT Medical Descriptors:

chemical reaction  
reaction analysis  
synthesis  
chemical structure  
structure analysis  
article

Drug Descriptors:

\*pyridazine derivative  
\*benzothiazole derivative  
\*benzimidazole derivative  
\*triazole derivative  
hydrazine derivative  
semicarbazide derivative  
hydrazide derivative  
thiophenol derivative  
phenylenediamine derivative

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ACCESSION NUMBER: 2005412832 EMBASE Full-text

TITLE: Heterocyclic synthesis with nitriles: Synthesis of some new thiophene, pyridazine, oxazine, thiopyran, pyrrole, and pyrrolo[1,2-b]pyridazine derivatives.

AUTHOR: Abdelrazek F.M.

CORPORATE SOURCE: F.M. Abdelrazek, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt. prof\_fmrazek@yahoo.com

SOURCE: Synthetic Communications, (2005) Vol. 35, No. 17, pp. 2251-2258. .

Refs: 15

ISSN: 0039-7911 CODEN: SYNCAV

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 13 Oct 2005

Last Updated on STN: 13 Oct 2005

ED Entered STN: 13 Oct 2005

Last Updated on STN: 13 Oct 2005

AB 2-Phenyl-1,1,3-tricyanopropene [ $\alpha$ -(cyanomethyl)benzylidene- malononitrile] undergoes bromination with N-bromosuccinimide (NBS) to afford 2-phenyl-1,1,3-tricyano-3-bromopropene: [ $\alpha$ -(bromocyanomethyl)benzylidene malononitrile]. This bromo derivative undergoes reactions with sodium hydrogen sulfide, hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, ethyl thioglycollate, urea derivatives, and cyanacetohydrazide to afford thiophene, 4H-pyridazines, 4H-oxazine and 4H-thiopyran, N-substituted pyrrole, and pyrrolo[1,2-b]pyridazine derivatives respectively. Copyright .COPYRGT. Taylor & Francis, Inc.

CT Medical Descriptors:  
 bromination  
 synthesis  
 reaction analysis  
 proton nuclear magnetic resonance  
 carbon nuclear magnetic resonance  
 article  
 Drug Descriptors:  
\*thiophene derivative  
\*pyridazine derivative  
 \*oxazine derivative  
 \*thiopyran derivative  
 \*pyrrole derivative  
 \*pyrrolo[1,2 b]pyridazine  
 nitrile  
 2 phenyl 1,1,3 tricyanopropene  
 n bromosuccinimide  
 2 phenyl 1,1,3 tricyano 3 bromopropene  
 hydrogen sulfide  
 hydrazine  
 phenylhydrazine  
 hydroxylamine  
 thioglycolic acid  
 urea derivative  
 acetohydrazide  
 4h pyridazine derivative  
 4h oxazine derivative  
 4h thiopyran derivative  
 unclassified drug

RN (n bromosuccinimide) 128-08-5, 39660-53-2; (hydrogen sulfide) 15035-72-0, 7783-06-4; (hydrazine) 10217-52-4, 13775-80-9, 18500-32-8, 302-01-2, 7803-57-8; (phenylhydrazine) 100-63-0, 59-88-1; (hydroxylamine) 7803-49-8; (thioglycolic acid) 68-11-1; (acetohydrazide) 1068-57-1

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ACCESSION NUMBER: 2003167102 EMBASE Full-text  
 TITLE: Solid-phase synthesis of heterocycles from 1,4-diketone synthons.  
 AUTHOR: Raghavan S.; Anuradha K.  
 CORPORATE SOURCE: S. Raghavan, Organic Division I, Indian Inst. of Chemical Technology, Hyderabad 500 007, India. purush101@yahoo.com  
 SOURCE: Synlett, (2003) No. 5, pp. 711-713. .  
 Refs: 21  
 ISSN: 0936-5214 CODEN: SYNLES  
 COUNTRY: Germany  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 029 Clinical Biochemistry  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 19 May 2003  
 Last Updated on STN: 19 May 2003

ED Entered STN: 19 May 2003

Last Updated on STN: 19 May 2003

AB The solid-phase synthesis of furans, thiophenes, pyrroles and pyridazines from 1,4-diketones as the common intermediate is reported. A diverse collection of these heterocyclic compounds is readily prepared in two high yielding steps.

CT Medical Descriptors:  
 synthesis  
 chemical reaction

chemical structure  
 solid  
 article  
 Drug Descriptors:  
 \*furan derivative  
 \*thiophene derivative  
 \*pyrrole derivative  
 \*pyridazine derivative  
 \*1,4 diketone

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ACCESSION NUMBER: 2002291955 EMBASE Full-text

TITLE: Dramatically enhanced fluorescence of heteroaromatic chromophores upon insertion as spacers into oligo(triacetylene)s.

AUTHOR: Edelmann M.J.; Raimundo J.-M.; Utesch N.F.; Diederich F.; Boudon C.; Gisselbrecht J.-P.; Gross M.

CORPORATE SOURCE: F. Diederich, Laboratorium fur Organische Chemie, ETH-Honggerberg, HCI, CH-8093 Zurich, Switzerland

SOURCE: Helvetica Chimica Acta, (2002) Vol. 85, No. 7, pp. 2195-2213. .

Refs: 44

ISSN: 0018-019X CODEN: HCACAV

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 29 Aug 2002

Last Updated on STN: 29 Aug 2002

ED Entered STN: 29 Aug 2002

Last Updated on STN: 29 Aug 2002

AB In continuation of a previous study on the modulation of  $\pi$ -electron conjugation of oligo(triacetylene)s by insertion of central hetero-spacer fragments between two (E)-hex-3-ene-1,5-diyne ((E)-1,2-diethynylethene, DEE) moieties (Fig. 1), a new series of trimeric hybrid oligomers (14-18 and 22-24, Fig. 2) were prepared (Schemes 1-3). Spacers used were both electron-deficient (quinoxaline-based heterocycles, pyridazine) and electron-rich (2,2'-bithiophene, 9,9-dioctyl-9H-fluorene) chromophores. With 19-21 (Scheme 4), a series of transition metal complexes was synthesized as potential precursors for nanoscale scaffolding based on both covalent acetylenic coupling and supramolecular assembly. The UV/VIS spectra (Fig. 3) revealed that the majority of spacers provided heterotrimers featuring extended  $\pi$ -electron delocalization. The new hybrid chromophores show a dramatically enhanced fluorescence compared with the DEE dimer 13 and homo-trimer 12 (Fig. 5). This increase in emission intensity appears as a general feature of these systems: even if the spacer molecule is non-fluorescent, the corresponding hetero-trimer may show a strong emission (Table 2). The redox properties of the new hybrid chromophores were determined by cyclic voltammetry (CV) and rotating-disk voltammetry (RDV) (Table 3 and Fig. 5). In each case, the first one-electron reduction step in the hetero-trimers appeared anodically shifted compared with DEE dimer 13 and homo-trimer 12. With larger spacer chromophore extending into two dimensions (as in 14-18, Fig. 2), the anodic shift (by 240-490 mV, Table 3) seems to originate from inductive effects of the two strongly electron-accepting DEE substituents rather than from extended  $\pi$ -electron conjugation along the oligomeric backbone, as had previously been observed for DEE-substituted porphyrins.

CT Medical Descriptors:

\*fluorescence  
 chromatophore  
 gene insertion  
 electron  
 hybridization  
 synthesis  
 supramolecular chemistry  
 ultraviolet spectroscopy  
 dimerization  
 oxidation reduction reaction  
 cyclic potentiometry  
 article  
 priority journal  
 Drug Descriptors:  
 \*oligo(triacetylene) derivative  
 \*acetylene derivative  
 hex 3 ene 1,5 diyne  
 1,2 diethynylethene  
 ethylene derivative  
 quinoxaline derivative  
pyridazine derivative  
2,2' bithiophene 9,9 dioctyl 9h fluorene  
 fluorene derivative  
 metal complex  
 porphyrin derivative  
 unclassified drug

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ACCESSION NUMBER: 96172203 EMBASE Full-text

DOCUMENT NUMBER: 1996172203

TITLE: Amide anions as unexpected activating groups in nucleophilic heteroaromatic substitution.

AUTHOR: Gillies I.; Rees C.W.

CORPORATE SOURCE: Process Research and Development, Glaxo Wellcome Plc, Temple Hill, Dartford, Kent DA1 5AH, United Kingdom

SOURCE: Tetrahedron Letters, (1996) Vol. 37, No. 23, pp. 4065-4068.

ISSN: 0040-4039 CODEN: TELEAY

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 8 Jul 1996

Last Updated on STN: 8 Jul 1996

ED Entered STN: 8 Jul 1996

Last Updated on STN: 8 Jul 1996

AB Nucleophilic displacement of halide by alkoxide in pyridazines, phthalazines, a thiazole and a thiadiazole is unexpectedly activated by acetamido anion substituents compared to neutral amido and amino substituents.

CT Medical Descriptors:

\*drug synthesis

article

reaction analysis

stereochemistry

Drug Descriptors:

\*pyridazine derivative: AN, drug analysis

\*pyridazine derivative: DV, drug development

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ACCESSION NUMBER: 94341889 EMBASE Full-text

DOCUMENT NUMBER: 1994341889

TITLE: A new entry to the ethynylation of azaaromatics using bis(tributylstannyl)acetylene in the presence of alkyl chloroformate.

AUTHOR: Itoh T.; Hasegawa H.; Nagata K.; Okada M.; Ohsawa A.

CORPORATE SOURCE: School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan

SOURCE: Tetrahedron, (1994) Vol. 50, No. 46, pp. 13089-13100. .  
ISSN: 0040-4020 CODEN: TETRAB

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 7 Dec 1994

Last Updated on STN: 7 Dec 1994

ED Entered STN: 7 Dec 1994

Last Updated on STN: 7 Dec 1994

AB Unstable N-alkoxycarbonyl quaternary salts of azaaromatics were trapped in situ by bis(tributylstannyl)acetylene followed by the treatment with trifluoroacetic acid to give 2-ethynyl adducts in good yields. The same compounds were obtained only in low yields when ethynyltributyltin was used as a nucleophile. The reaction was revealed to be available for various aromatics including pyridine, pyridazine, imidazole, thiazole, oxazole, and benzodiazines.

CT Medical Descriptors:

\*drug synthesis

article

methodology

priority journal

reaction analysis

Drug Descriptors:

\*imidazole derivative: AN, drug analysis

\*imidazole derivative: DV, drug development

\*isoquinoline derivative: AN, drug analysis

\*isoquinoline derivative: DV, drug development

\*oxazole derivative: AN, drug analysis

\*oxazole derivative: DV, drug development

\*pyridazine derivative: AN, drug analysis

\*pyridazine derivative: DV, drug development

\*pyridine derivative: DV, drug development

\*pyridine derivative: AN, drug analysis

\*quinoline derivative: AN, drug analysis

\*quinoline derivative: DV, drug development

\*quinoxaline derivative: AN, drug analysis

\*quinoxaline derivative: DV, drug development

\*thiazole derivative: AN, drug analysis

\*thiazole derivative: DV, drug development

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ACCESSION NUMBER: 95163531 EMBASE Full-text

DOCUMENT NUMBER: 1995163531

TITLE: Heterocyclic synthesis with nitriles: New routes for synthesis of pyridazines, pyridines and their fused derivatives.

AUTHOR: Negm A.M.; Abdelrazek F.M.; Elnagdi M.H.; Shaaban L.H.

CORPORATE SOURCE: Chemistry Department, Faculty of Science, Cairo  
University, Giza, Egypt  
SOURCE: Archives of Pharmacal Research, (1994) Vol. 17, No. 6, pp.  
411-414. .  
ISSN: 0253-6269 CODEN: APHRDQ  
COUNTRY: Korea, Republic of  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 27 Jun 1995  
Last Updated on STN: 27 Jun 1995

ED Entered STN: 27 Jun 1995

Last Updated on STN: 27 Jun 1995

AB Phenylazocyanothioacetamide 1 reacts with malononitrile to afford the pyridinethione 4 which reacts with phenacylbromide to yield the pyridine-S-phenacyl derivative 6. 1 reacts with ethyl cyanoacetate to yield the pyridazine derivative, 8, and with phenacyl bromide to afford the N-phenacyl derivative 11, instead of the thiazole 10. Compound 11 afforded the pyrazolopyridine 13 on reaction with malononitrile while 10 was obtained on coupling of the thiazole 14 with diazotised aniline. Compound 10 reacts with malononitrile to afford the thiazolyl pyridazine 15. Compound 1 reacts with malononitrile dimer to afford the pyridopyridazine derivative 17a. 1 reacts also with active methylene heterocycles to afford the pyrazolo and thiazolo-fused pyridazines 20 and 23 respectively.

CT Medical Descriptors:

\*drug synthesis

article

methodology

reaction analysis

Drug Descriptors:

\*pyridazine derivative: AN, drug analysis

\*pyridazine derivative: DV, drug development

\*pyridine derivative: DV, drug development

\*pyridine derivative: AN, drug analysis

\*thiazole derivative: DV, drug development

\*thiazole derivative: AN, drug analysis

pyrazolo[3,4 c]pyrazole derivative: DV, drug development

pyrazolo[3,4 c]pyrazole derivative: AN, drug analysis

pyrazolo[4,3 b]pyridine derivative: AN, drug analysis

pyrazolo[4,3 b]pyridine derivative: DV, drug development

pyrido[2,3 d]pyridazine derivative: AN, drug analysis

pyrido[2,3 d]pyridazine derivative: DV, drug development

thiazolo[4,5 c]pyridazine derivative: AN, drug analysis

thiazolo[4,5 c]pyridazine derivative: DV, drug development

unclassified drug

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ACCESSION NUMBER: 94246476 EMBASE Full-text

DOCUMENT NUMBER: 1994246476

TITLE: Hydralazine and other hydrazine derivatives and the formation of DNA adducts.

AUTHOR: Mathison B.H.; Murphy S.E.; Shank R.C.

CORPORATE SOURCE: Environmental Toxicology Program, Community/Environmental Med. Dept., University of California, Irvine, CA 92717, United States

SOURCE: Toxicology and Applied Pharmacology, (1994) Vol. 127, No. 1, pp. 91-98. .  
ISSN: 0041-008X CODEN: TXAPA

COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 7 Sep 1994  
 Last Updated on STN: 7 Sep 1994

ED Entered STN: 7 Sep 1994

Last Updated on STN: 7 Sep 1994

AB Previous work has demonstrated that hydrazine after formylation to its corresponding hydrazone may be activated both in vivo and in vitro to a methylating intermediate resulting in the formation of O6-methyl- and N7-methylguanines in DNA. Incubation of calf thymus DNA with the hydrazine derivative, hydralazine, and formaldehyde resulted in the production of N7-methylguanine and two aberrant bases in DNA. These bases were separated by strong cation-exchange high-performance liquid chromatographic fractionation of neutral thermal hydrolysates. Administration of hydralazine to rats resulted in the formation of N7-methylguanine in liver DNA, but the two unknown bases observed in the in vitro experiment could not be demonstrated in vivo. In contrast to hydrazine, administration of hydralazine resulted in the methylation of DNA only at doses approaching the LD50, suggesting that formylation does not represent a significant mechanism for hydralazine toxicity in the system described. Hydralazine in combination with formaldehyde resulted in the formation of triazolophthalazine, a metabolite which has been characterized in man. The ability of 17 other hydrazine derivatives to alkylate liver DNA was determined after single administration to young adult male Sprague-Dawley rats or C57BL6 mice. Quantifiable amounts of N7-methylguanine were measured in liver DNA from animals treated with 10 of the 17 compounds. In 3 of the 10 cases quantifiable amounts of O6-methylguanine were also measured. Methylation of liver DNA guanine was obtained with hydrazine, hydralazine, procarbazine, isoniazid, phenylhydrazine, nialamide, nitrofurazone, maleic hydrazide, sulfomethoxypyridazine, and sulfamethiazole and two hydrazine-formaldehyde polymerization products, formalazine and tetraformyltrisazine.

CT Medical Descriptors:

\*dna adduct  
 \*dna methylation  
 \*drug dna interaction  
 article  
 dna alkylation  
 dose response  
 Drug Descriptors:  
 \*7 methylguanine  
 \*formaldehyde  
 \*hydralazine  
 drug metabolite  
 formalazine  
 hydrazine  
 hydrazine derivative  
 isoniazid  
maleic hydrazide  
 nialamide  
 nitrofurazone  
 phenylhydrazine  
 procarbazine  
 sulfamethiazole  
 sulfamethoxypyridazine  
 tetraformyltrisazine  
 triazolophthalazine

unclassified drug  
 RN (7 methylguanine) 578-76-7; (formaldehyde) 50-00-0; (hydralazine) 304-20-1, 86-54-4; (hydrazine) 10217-52-4, 13775-80-9, 18500-32-8, 302-01-2, 7803-57-8; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (maleic hydrazide) 123-33-1; (nialamide) 51-12-7; (nitrofural) 59-87-0; (phenylhydrazine) 100-63-0, 59-88-1; (procarbazine) 366-70-1, 671-16-9; (sulfamethizole) 144-82-1; (sulfamethoxypyridazine) 80-35-3  
 CO Sigma (United States); Aldrich (United States)

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ACCESSION NUMBER: 93203344 EMBASE Full-text  
 DOCUMENT NUMBER: 1993203344  
 TITLE: The induction of cytochrome P4502E1 by nitrogen- and sulfur-containing heterocycles: Expression and molecular regulation.  
 AUTHOR: Sang Geon Kim; Novak R.F.  
 CORPORATE SOURCE: Institute of Chemical Toxicology, Wayne State University, Detroit, MI 48201, United States  
 SOURCE: Toxicology and Applied Pharmacology, (1993) Vol. 120, No. 2, pp. 257-265. .  
 ISSN: 0041-008X CODEN: TXAPA  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 029 Clinical Biochemistry  
 052 Toxicology  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 15 Aug 1993  
 Last Updated on STN: 15 Aug 1993

ED Entered STN: 15 Aug 1993

Last Updated on STN: 15 Aug 1993

AB Several structurally related sulfur- and nitrogen-containing heterocycles including thiazole, pyrazine, pyridazine, pyrimidine, thiophene, and triazole, which are present in tobacco, tobacco smoke, and certain foods, have been employed with the goal of characterizing the effects of these agents on the inhibition and expression of P4502E1 in hepatic tissue and on the molecular level regulatory events governing enhanced expression. The results of this study reveal that whereas the binding constants of these compounds to 2E1 moderately correlated with the percentage inhibition of metabolic activity in vitro ( $r = 0.66$ ), neither inhibition of metabolic activity nor binding to P4502E1 correlated with relative induction of P4502E1 levels ( $r = 0.07$  and  $0.03$ , respectively). Thiazole, which produced the greatest inhibition of metabolic activity (88%) and exhibited the highest binding affinity for P4502E1 (35  $\mu\text{M}$ ), induced P4502E1 .apprx.fourfold. In contrast, pyrazine and pyridazine, which only marginally inhibited metabolic activity (54 and 41%, respectively), and weakly bound 2E1 (73 and 384  $\mu\text{M}$ , respectively), increased P4502E1 levels .apprx.four- and fivefold, respectively. A common feature associated with these inducers, however, was the substantial decrease in hepatic P4502E1 poly(A)+ RNA levels in treated animals relative to untreated animals. Slot and Northern blot hybridization analyses revealed an .apprx.80% decrease in P4502E1 poly(A)+ RNA levels at 48 hr following treatment of rats with thiazole, and at 24 hr following treatment of animals with either pyrazine or pyridazine, relative to controls. P4502E1 poly(A)+ RNA levels appeared to increase gradually, returning to levels which approximated 60% of the P4502E1 poly(A)+ RNA levels present in untreated animals at 48 and 72 hr following treatment with pyrazine or pyridazine, respectively. The results of these experiments show that thiazole, pyrazine, and pyridazine induce P4502E1 in rats, that the induction of 2E1 is associated with a concomitant decrease

in 2E1 poly(A)+ RNA levels, and that these agents differentially affect the expression of P4502E1.

## CT Medical Descriptors:

\*enzyme induction  
 \*enzyme inhibition  
 animal tissue  
 article  
 controlled study  
 male

nonhuman

priority journal

rat

## Drug Descriptors:

\*cytochrome p450 isoenzyme: EC, endogenous compound

\*pyrazine

\*pyrazole

\*pyridazine

\*pyridine

\*pyrimidine

\*thiazole

\*thiophene

\*triazole

rna: EC, endogenous compound

RN (pyrazine) 290-37-9; (pyrazole) 288-13-1; (pyridazine) 289-80-5;  
 (pyridine) 110-86-1; (pyrimidine) 289-95-2; (thiazole) 288-47-1;  
 (thiophene) 110-02-1; (triazole) 37306-44-8; (rna) 63231-63-0

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ACCESSION NUMBER: 92351768 EMBASE Full-text

DOCUMENT NUMBER: 1992351768

TITLE: Condensation of muscimol or thiomuscimol with aminopyridazines yields GABA-A antagonists.

AUTHOR: Melikian A.; Schlewer G.; Chambon J.-P.; Wermuth C.G.

CORPORATE SOURCE: Lab. de Pharmacochimie Molculaire, Centre de Neurochimie du CNRS, 5, Rue Blaise Pascal, 67084 Strasbourg, France

SOURCE: Journal of Medicinal Chemistry, (1992) Vol. 35, No. 22, pp. 4092-4097.

ISSN: 0022-2623 CODEN: JMCMAR

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20 Dec 1992

Last Updated on STN: 20 Dec 1992

ED Entered STN: 20 Dec 1992

Last Updated on STN: 20 Dec 1992

AB Ten analogs of muscimol and thiomuscimol in which the amino function was delocalized in an amidinic system were prepared by N2 alkylation of 6-aryl-3-aminopyridazines with (chloromethyl)isoxazole or (chloromethyl)isothiazole derivatives. These muscimol and thiomuscimol derivatives show potent binding properties for GABA-A receptors (they displace [3H]GABA and [3H]gabazine) and provoke convulsions after iv injections. They fit well with the model pharmacophore proposed by our group for the GABA-A antagonists and show similar structure-activity profiles to that of the pyridazinyl-GABAs.

## CT Medical Descriptors:

\*drug mixture

\*drug synthesis

animal experiment  
 article  
 convulsion: ET, etiology  
 drug effect  
 drug receptor binding  
 mouse  
 nonhuman  
 priority journal  
 receptor affinity  
 structure activity relation  
 Drug Descriptors:  
 \*4 aminobutyric acid a receptor  
 \*4 aminobutyric acid  
 \*muscimol: CB, drug combination  
 \*muscimol: DV, drug development  
 \*muscimol: PD, pharmacology

\*pyridazine derivative: CB, drug combination

\*pyridazine derivative: DV, drug development

\*pyridazine derivative: PD, pharmacology

\*thiomuscimol: CB, drug combination

\*thiomuscimol: DV, drug development

\*thiomuscimol: PD, pharmacology

RN (4 aminobutyric acid) 28805-76-7, 56-12-2; (muscimol) 2763-96-4;  
 (thiomuscimol) 62020-54-6

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ACCESSION NUMBER: 92285548 EMBASE Full-text

DOCUMENT NUMBER: 1992285548

TITLE: [Heterocycles, LXVIII: Synthesis and reaction of some  
 2-aryl-5-R-1,2,4-triazolo[2',3':3,2] thiazolo  
 [4,5-d] pyridazines].  
 HETEROCYCLEN, 68. MITT.: DARSTELLUNG UND VERHALTEN EINIGER  
 2-ARYL-5-R-1,2,4-TRIAZOLO[2',3':3,2] - THIAZOLO  
 [4,5-D] PYRIDAZINE.

AUTHOR: Simiti I.; Zaharia V.; Demian H.

CORPORATE SOURCE: Univ. fur Medizin und Pharmazie, Fakultat fur Pharmazie,  
 Laboratorium fur Organische Chemie, V. Babes-Strasse  
 41,3400 Cluj-Napoca, Romania

SOURCE: Archiv der Pharmazie, (1992) Vol. 325, No. 9, pp. 609-611.

ISSN: 0365-6233 CODEN: ARPMAS

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

LANGUAGE: German

ENTRY DATE: Entered STN: 25 Oct 1992

Last Updated on STN: 25 Oct 1992

ED Entered STN: 25 Oct 1992

Last Updated on STN: 25 Oct 1992

CT Medical Descriptors:

\*synthesis

article

reaction analysis

Drug Descriptors:

\*1,2,4 triazole derivative: AN, drug analysis

\*1,2,4 triazole derivative: DV, drug development

\*pyridazine derivative: AN, drug analysis

\*pyridazine derivative: DV, drug development

\*thiazole derivative: AN, drug analysis

\*thiazole derivative: DV, drug development  
1,2,4 triazolo[2',3':3,2]thiazolo[4,5 d]pyridazine derivative: AN,  
drug analysis  
1,2,4 triazolo[2',3':3,2]thiazolo[4,5 d]pyridazine derivative: DV,  
drug development  
 unclassified drug

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ACCESSION NUMBER: 80187142 EMBASE Full-text  
 DOCUMENT NUMBER: 1980187142  
 TITLE: Studies on cardiovascular agents. VI. Synthesis and coronary vasodilating and antihypertensive activities of 1,2,4-triazolo [1,5-a]pyrimidines fused to heterocyclic systems.  
 AUTHOR: Sato Y.; Shimoji Y.; Fujita H.; et al.  
 CORPORATE SOURCE: Cent. Res. Lab., Sankyo Co. Ltd, Tokyo, Japan  
 SOURCE: Journal of Medicinal Chemistry, (1980) Vol. 23, No. 8, pp. 927-937.  
 CODEN: JMCMAR  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal  
 FILE SEGMENT: 037 Drug Literature Index  
 030 Pharmacology  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 9 Dec 1991  
 Last Updated on STN: 9 Dec 1991

ED Entered STN: 9 Dec 1991  
 Last Updated on STN: 9 Dec 1991

AB The synthesis and coronary vasodilating and antihypertensive activities of 1,2,4-triazolo[1,5-a]pyrimidines fused to pyrrole, thiophene, pyran, pyridine, and pyridazine are described. Among these compounds, 8-tert-butyl-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-a]pyrimidine was found to be the most promising potential cardiovascular agent, having been shown to be more potent in coronary vasodilating activity than trapidil [7-(diethylamino)-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine] and approximately equipotent to guanethidine sulfate in antihypertensive activity.

CT Medical Descriptors:  
 \*1,2,4 triazolo[1,5 a]pyrimidine derivative  
 \*bumepidil  
 \*blood pressure  
 \*coronary artery dilatation  
 \*dog  
 \*drug analysis  
 \*drug comparison  
 \*drug screening  
 \*drug synthesis  
 \*guinea pig  
 \*heart  
 \*hypertension  
 \*pharmacokinetics  
 \*rat  
 \*structure activity relation  
 \*vasodilatation  
 mass spectrometry  
 nuclear magnetic resonance  
 spontaneously hypertensive rat  
 ultraviolet spectrophotometry  
 cardiovascular system

in vitro study  
 theoretical study  
 animal experiment  
 oral drug administration  
 intravenous drug administration  
 intraarterial drug administration  
 Drug Descriptors:

\*pyran

\*pyridazine

\*pyridine

\*thiophene

guanethidine

trapidil

RN (pyran) 289-66-7, 33941-07-0; (pyridazine) 289-80-5; (pyridine) 110-86-1;  
 (thiophene) 110-02-1; (guanethidine) 55-65-2, 60-02-6, 645-43-2;  
 (trapidil) 15421-84-8

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ACCESSION NUMBER: 78125140 EMBASE Full-text

DOCUMENT NUMBER: 1978125140

TITLE: Chlorophenyl derivatives of pyridazine 3,6 dione.

AUTHOR: Baloniak S.; Mroczkiewicz A.

CORPORATE SOURCE: Zakl. Chem. Org., Inst. Chem. Anal., Akad. Med., Poznan, Poland

SOURCE: Annales Pharmaceutici, (1977) Vol. Vol.12, pp. 65-69. .  
 CODEN: APMCB4

COUNTRY: Poland

DOCUMENT TYPE: Journal

FILE SEGMENT: 037 Drug Literature Index  
 030 Pharmacology

LANGUAGE: Polish

SUMMARY LANGUAGE: English

CT Medical Descriptors:

\*4 alkoxy 2 (4 chlorophenyl) 2 methylpyridazine 3,6 dione

\*6 (3 chlorophenyl) 5 methylpyridazino[4,5 d]thiazolidine

\*bacterium

\*drug analysis

\*drug identification

\*drug screening

\*drug synthesis

\*microorganism

theoretical study

in vitro study

Drug Descriptors:

\*pyridazinone derivative

L99 ANSWER 69 OF 69 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 1984-35573 DRUGU E Full-text

TITLE: Pharmacological Influence on the Balance of Thromboxane and Prostacyclin in the Organism.

AUTHOR: Lakin K M; Makarov V A; Novikova N V; Tretyak V M; Rukazenzov Y E

LOCATION: Moscow, Russia

SOURCE: Farmakol.Toksikol. (47, No. 2, 67-79, 1984) 220 Ref.  
 CODEN: FATOAO

AVAIL. OF DOC.: N.A. Semashko Moscow Med. Sci. Inst., Moscow, U.S.S.R.

LANGUAGE: Russian

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Substances and mechanisms having effects on the balance between thromboxane A2 and prostacyclin are reviewed in relation to their formation and action in the body.

AN 1984-35573 DRUGU E Full-text

E Endocrinology

13 Endocrinology

CT REVIEW \*FT

- [01] THROMBOXANE-A2 \*FT; PROSTACYCLIN \*FT; PROSTAGLANDIN-METAB. \*FT; BIOSYNTH. \*FT; MAIN-TOPIC \*FT; PH \*FT
- [02] THROMBIN \*PH; CALCIMYCIN \*PH; CYCLOHEXIMIDE \*PH; ANGIOTENSIN-2 \*PH; OXYTOCIN \*PH; AMINAZINE \*PH; PROPRANOLOL \*PH; CYCLIC-AMP \*PH; PAPAVERINE \*PH; NICERGOLINE \*PH; MEPACRINE \*PH; ORGOTEIN \*PH; ASPIRIN \*PH; INDOMETACIN \*PH; PARACETAMOL \*PH; IBUPROFEN \*PH; VOLTAREN \*PH; PHENYLHYDRAZINE \*PH; GUAIACOL \*PH; NAPROXEN \*PH; FLURBIPROFEN \*PH; MEFENAMATE \*PH; SULINDAC \*PH; ESTRADIOL \*PH; ADRENALINE \*PH; SEROTONIN \*PH; UK-80338 \*PH; UK-34787 \*PH; DAZOXIBEN \*PH; BURIMAMIDE \*PH; NICOTINATE \*PH; OKY-1581 \*PH; NICTINDOLE \*PH; OKY -1580 \*PH; EPL-55712 \*PH; N-0164 \*PH; TLCK \*PH; TOCOPHEROL \*PH; HYDRALAZINE \*PH; CHLORPROMAZINE \*PH; DICLOFENAC \*PH; PH \*FT
- [03] DIPYRIDAMOLE \*PH; DIAZOXIDE \*PH; NICOTINE \*PH; PENTOXIFYLLINE \*PH; CLOFIBRATE \*PH; PAPAVERINE \*PH; NITROGLYCEROL \*PH; NITROPRUSSIDE \*PH; CLONIDINE \*PH; VERAPAMIL \*PH; DIHYDRALAZINE \*PH; DEFIBROTIDE \*PH; FUROSEMIDE \*PH; ESTRADIOL \*PH; NIFEDIPINE \*PH; ASPIRIN \*PH; TRAPYMIN \*PH; NAFAZATROM \*PH; PH \*FT

=&gt; d que nos 136

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L5      STR
L7      21 SEA FILE=REGISTRY SSS FUL L5
L13     STR
L15     85 SEA FILE=REGISTRY SSS FUL L13
L17     QUE ABB=ON PLU=ON EGGENWEILER, H?/AU
L18     QUE ABB=ON PLU=ON WOLF, M?/AU
L19     QUE ABB=ON PLU=ON MERCK/PA,CS,SO
L29     1 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L30     32 SEA FILE=HCAPLUS ABB=ON PLU=ON L15
L31     32 SEA FILE=HCAPLUS ABB=ON PLU=ON (L29 OR L30)
L36     3 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND (L17 OR L18 OR L19)

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=&gt; d que nos 147

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L5      STR
L7      21 SEA FILE=REGISTRY SSS FUL L5
L13     STR
L15     85 SEA FILE=REGISTRY SSS FUL L13
L17     QUE ABB=ON PLU=ON EGGENWEILER, H?/AU
L18     QUE ABB=ON PLU=ON WOLF, M?/AU
L19     QUE ABB=ON PLU=ON MERCK/PA,CS,SO
L44     1 SEA FILE=TOXCENTER ABB=ON PLU=ON L7
L45     6 SEA FILE=TOXCENTER ABB=ON PLU=ON L15
L46     6 SEA FILE=TOXCENTER ABB=ON PLU=ON (L44 OR L45)
L47     1 SEA FILE=TOXCENTER ABB=ON PLU=ON L46 AND (L17 OR L18 OR L19)

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=&gt; d que nos 162

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L13     STR
L17     QUE ABB=ON PLU=ON EGGENWEILER, H?/AU
L18     QUE ABB=ON PLU=ON WOLF, M?/AU
L19     QUE ABB=ON PLU=ON MERCK/PA,CS,SO
L55     35 SEA FILE=WPIX SSS FUL L13
L56     11 SEA FILE=WPIX ABB=ON PLU=ON (RACQNP/DCN OR RACVZA/DCN OR
RACVZB/DCN OR RACVZC/DCN OR RACVZD/DCN OR RACVZE/DCN OR
RACVZF/DCN OR RACVZG/DCN OR RACVZH/DCN OR RACVZI/DCN OR
RACVZM/DCN OR RACVZN/DCN OR RACVZO/DCN OR RACVZP/DCN OR
RACVZ3/DCN OR RACVZ4/DCN OR RACVZ5/DCN OR RACVZ6/DCN OR
RACVZ7/DCN OR RACVZ8/DCN OR RACVZ9/DCN OR RANV5C/DCN OR
RANV5G/DCN OR RANV5P/DCN OR RANV5Q/DCN OR RANV6F/DCN OR
RANV66/DCN OR RA1KDF/DCN OR RA1RZ6/DCN OR RA4W3Q/DCN OR
RA4XH0/DCN OR RA4X3I/DCN OR RA4X4A/DCN OR RA4X4D/DCN OR
RA6SZ8/DCN)
L57     11 SEA FILE=WPIX ABB=ON PLU=ON L55/DCR
L58     11 SEA FILE=WPIX ABB=ON PLU=ON (L56 OR L57)
L59     QUE ABB=ON PLU=ON F530/M0,M1,M2,M3,M4,M5,M6
L61     635 SEA FILE=WPIX ABB=ON PLU=ON (L58 OR L59) AND (L17 OR L18 OR
L19)
L62     1 SEA FILE=WPIX ABB=ON PLU=ON L61 AND L58

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=&gt; d que 172

```

L17     QUE ABB=ON PLU=ON EGGENWEILER, H?/AU
L18     QUE ABB=ON PLU=ON WOLF, M?/AU
L19     QUE ABB=ON PLU=ON MERCK/PA,CS,SO
L28     QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?

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10/518,503

L65           QUE   ABB=ON   PLU=ON   PYRIDAZINES+PFT,OLD,NEW,NT/CT  
L66           QUE   ABB=ON   PLU=ON   THIOPHENES+PFT,OLD,NEW,NT/CT  
L67           QUE   ABB=ON   PLU=ON   THIAZOLES+PFT,OLD,NEW,NT/CT  
L68           257 SEA FILE=MEDLINE ABB=ON   PLU=ON   L65 AND (L66 OR L67 OR L28)  
L72           2   SEA FILE=MEDLINE ABB=ON   PLU=ON   L68 AND (L17 OR L18 OR L19)

=> d que 188

L17           QUE   ABB=ON   PLU=ON   EGGENWEILER, H?/AU  
L18           QUE   ABB=ON   PLU=ON   WOLF, M?/AU  
L19           QUE   ABB=ON   PLU=ON   MERCK/PA,CS,SO  
L28           QUE   ABB=ON   PLU=ON   ?THIAZOL? OR ?THIOPHEN?  
L73           QUE   ABB=ON   PLU=ON   "PYRIDAZINE DERIVATIVE"+PFT,OLD,NEW,  
              NT/CT  
L74           QUE   ABB=ON   PLU=ON   "PYRIDAZINONE DERIVATIVE"+PFT,OLD,NE  
              W,NT/CT  
L75           QUE   ABB=ON   PLU=ON   "THIAZOLE DERIVATIVE"+PFT,OLD,NEW,NT  
              /CT  
L76           QUE   ABB=ON   PLU=ON   "THIOPHENE DERIVATIVE"+PFT,OLD,NEW,N  
              T/CT  
L77           217 SEA FILE=EMBASE ABB=ON   PLU=ON   (L73 OR L74) AND ((L75 OR L76)  
              OR L28)  
L88           3   SEA FILE=EMBASE ABB=ON   PLU=ON   L77 AND (L17 OR L18 OR L19)

=> d his 193

(FILE 'BIOSIS, PASCAL, JICST-EPLUS, JAPIO, LIFESCI, BIOENG, BIOTECHNO,  
BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED  
AT 12:26:38 ON 20 DEC 2006)

L93           1 S L91 AND L19-L20

=> d que 193

L19           QUE   ABB=ON   PLU=ON   MERCK/PA,CS,SO  
L20           QUE   ABB=ON   PLU=ON   (WOLF OR EGGENWEILER)/AU  
L27           QUE   ABB=ON   PLU=ON   ?PYRIDAZIN?  
L28           QUE   ABB=ON   PLU=ON   ?THIAZOL? OR ?THIOPHEN?  
L91           423 SEA L27(7A) L28  
L93           1   SEA L91 AND (L19 OR L20)

=> dup rem 136 147 162 172 188 193

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FILE 'BIOSIS' ENTERED AT 12:51:07 ON 20 DEC 2006  
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PROCESSING COMPLETED FOR L36  
 PROCESSING COMPLETED FOR L47  
 PROCESSING COMPLETED FOR L62  
 PROCESSING COMPLETED FOR L72  
 PROCESSING COMPLETED FOR L88  
 PROCESSING COMPLETED FOR L93

L100 9 DUP REM L36 L47 L62 L72 L88 L93 (2 DUPLICATES REMOVED)  
 ANSWERS '1-3' FROM FILE HCAPLUS  
 ANSWERS '4-5' FROM FILE MEDLINE  
 ANSWERS '6-8' FROM FILE EMBASE  
 ANSWER '9' FROM FILE BIOSIS

=> file stnguide

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 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Dec 19, 2006 (20061219/UP).

=> d ibib ed ab 1-9

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS' - CONTINUE?  
 (Y)/N:y

L100 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1  
 ACCESSION NUMBER: 2004:2882 HCAPLUS Full-text  
 DOCUMENT NUMBER: 140:77154  
 TITLE: Preparation of thiazoles as phosphodiesterase IV  
 inhibitors for the treatment of osteoporosis, tumors  
 and cachexia  
 INVENTOR(S): Egggenweiler, Hans-Michael; Wolf, Michael  
 PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany  
 SOURCE: PCT Int. Appl., 125 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000839	A1	20031231	WO 2003-EP4434	20030428
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
DE 10227269	A1	20040108	DE 2002-10227269	20020619
CA 2489902	A1	20031231	CA 2003-2489902	20030428
AU 2003232215	A1	20040106	AU 2003-232215	20030428
BR 2003011879	A	20050315	BR 2003-11879	20030428
EP 1513837	A1	20050316	EP 2003-760583	20030428

EP 1513837 B1 20060830  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 CN 1662529 A 20050831 CN 2003-814060 20030428  
 JP 2005530825 T 20051013 JP 2004-514623 20030428  
 AT 338041 T 20060915 AT 2003-760583 20030428  
 US 2005222160 A1 20051006 US 2004-518503 20041220  
 PRIORITY APPLN. INFO.: DE 2002-10227269 A 20020619  
 WO 2003-EP4434 W 20030428

OTHER SOURCE(S): MARPAT 140:77154

ED Entered STN: 02 Jan 2004

AB Title compds. I [R1, R2 = H, OH, OR8, etc.; R8 = A, cycloalkyl, alkenyl, etc.; R3 = H, A"R7, COA"R7, etc.; A = alkyl, alkenyl; R7 = H, CO2H, CONH2, etc.; A" = alkylene, alkenylene, cycloalkylene, etc.; V, W = O, OH with the proviso that if V = O, then W = H, H; B = (un)substituted aromatic isocyclic, heterocyclic e.g., pyridyl, pyridyl-N-oxide, thienyl, etc.; X = N, CR3] their pharmaceutically acceptable salts and formulations were prepared For example, coupling of acid chloride II, e.g., prepared from 4-methyl-2-pyridin-2-ylthiazole-5-carboxylic acid Me ester in 3-steps, and 3-(3-cyclopentyloxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine afforded claimed thiazole III. Compds. I are claimed useful as phosphodiesterase IV inhibitors (no data provided) for the treatment of osteoporosis, tumors, cachexia, etc.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:189365 HCAPLUS Full-text

DOCUMENT NUMBER: 139:78424

TITLE: Pyridazinones as selective cyclooxygenase-2 inhibitors

AUTHOR(S): Li, Chun Sing; Brideau, Christine; Chan, Chi Chung; Savoie, Chantal; Claveau, David; Charleson, Stella; Gordon, Robert; Greig, Gillian; Gauthier, Jacques Yves; Lau, Cheuk K.; Riendeau, Denis; Therien, Michel; Wong, Elizabeth; Prasit, Petpiboon

CORPORATE SOURCE: Merck Frosst Centre for Therapeutic

Research, Pointe-Claire-Dorval, QC, 1005, Can.  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(4), 597-600

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:78424

ED Entered STN: 11 Mar 2003

AB Pyridazinone was found to be an excellent core template for selective COX-2 inhibitors. Two potent, selective and orally active COX-2 inhibitors (I and II), which were highly efficacious in rat paw edema and rat pyresis models, have been obtained.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:635750 HCAPLUS Full-text

DOCUMENT NUMBER: 129:275920

TITLE: Preparation of pyridazinones as inhibitors of cyclooxygenase-2

INVENTOR(S): Li, Chun Sing; Prasit, Petpiboon; Gauthier, Jacques Y.; Lau, Cheuk K.; Therien, Michel

PATENT ASSIGNEE(S): Merck Frosst Canada Inc., Can.

SOURCE: PCT Int. Appl., 87 pp.

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841511	A1	19980924	WO 1998-CA233	19980312
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2283399	A1	19980924	CA 1998-2283399	19980312
CA 2283399	C	20060221		
AU 9864913	A	19981012	AU 1998-64913	19980312
AU 738727	B2	20010927		
EP 975604	A1	20000202	EP 1998-910544	19980312
EP 975604	B1	20040721		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001514669	T	20010911	JP 1998-539982	19980312
AT 271547	T	20040815	AT 1998-910544	19980312
ES 2224366	T3	20050301	ES 1998-910544	19980312
US 6004960	A	19991221	US 1998-42174	19980313
PRIORITY APPLN. INFO.:			US 1997-40791P	P 19970314
			GB 1997-7487	A 19970414
			WO 1998-CA233	W 19980312

OTHER SOURCE(S): MARPAT 129:275920

ED Entered STN: 08 Oct 1998

AB The title compds. [I; X = a bond, (CH<sub>2</sub>)<sub>m</sub> (m = 1-2); CO, etc.; R<sub>1</sub> = Me, NH<sub>2</sub>. NHC(O)CF<sub>3</sub>; R<sub>2</sub> = (CR<sub>6</sub>R<sub>7</sub>)nR<sub>8</sub> (R<sub>6</sub>, R<sub>7</sub> = H, C1-10 alkyl, C1-10 fluoroalkyl; R<sub>8</sub> = C1-10 alkyl, (un)substituted Ph, naphthyl, etc.); R<sub>3</sub> = C1-10 alkyl, (un)substituted Ph, naphthyl, etc.; R<sub>4</sub> = H, halo, C1-6 alkyl], useful in treating an inflammatory disease susceptible to treatment with a non-steroidal antiinflammatory agent, and cyclooxygenase-2 mediated diseases, were prepared Thus, reaction of 5-hydroxy-4-(4-methylsulfonyl)phenyl-3-phenyl-5H-furan-2-one with phenylhydrazine in EtOH afforded 30% I [X = a bond; R<sub>1</sub> = Me; R<sub>2</sub> = Ph; R<sub>3</sub> = Ph; R<sub>4</sub> = H] which showed IC<sub>50</sub> of 0.08 against COX-2 using CHO cell line assay.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 4 OF 9 MEDLINE on STN

ACCESSION NUMBER: 2000202347 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 10737739

TITLE: Molecular modeling of the aldose reductase-inhibitor complex based on the X-ray crystal structure and studies with single-site-directed mutants.

AUTHOR: Singh S B; Malamas M S; Hohman T C; Nilakantan R; Carper D A; Kitchen D

CORPORATE SOURCE: Wyeth Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000, National Eye Institute, NIH, Bethesda, Maryland 20892, USA.. [suresh.singh@merck.com](mailto:suresh.singh@merck.com)

SOURCE: Journal of medicinal chemistry, (2000 Mar 23) Vol. 43, No. 6, pp. 1062-70.  
 Journal code: 9716531. ISSN: 0022-2623.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200004  
 ENTRY DATE: Entered STN: 21 Apr 2000  
 Last Updated on STN: 21 Apr 2000  
 Entered Medline: 13 Apr 2000

ED Entered STN: 21 Apr 2000  
 Last Updated on STN: 21 Apr 2000  
 Entered Medline: 13 Apr 2000

AB Aldose reductase (AR) has been implicated in the etiology of the secondary complications of diabetes. This enzyme catalyzes the reduction of glucose to sorbitol using nicotinamide adenine dinucleotide phosphate as an essential cofactor. AR has been localized at the sites of tissue damage, and inhibitors of this enzyme prevent the development of neuropathy, nephropathy, retinopathy, and cataract formation in animal models of diabetes. The crystal structure of AR complexed with zopolrestat, a potent inhibitor of AR, has been described.(1) We have generated a model of the AR-inhibitor complex based on the reported Calpha coordinates of the protein and results of a structure-activity relationship study using four structurally distinct classes of inhibitors, recombinant human AR, and four single-site-directed mutants of this enzyme. The effects of the site-directed mutations on residues within the active site of the enzyme were evaluated by average interaction energy calculations and by calculations of carbon atom surface area changes. These values correlated well with the IC(50) values for zopolrestat with the wild-type and mutant enzymes, validating the model. On the basis of the zopolrestat-binding model, we have proposed binding models for 10 other AR inhibitors. Our models have enabled us to gain a qualitative understanding of the binding domains of the enzyme and how different inhibitors impact the size and shape of the binding site.

L100 ANSWER 5 OF 9 MEDLINE on STN  
 ACCESSION NUMBER: 1999083918 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 9866686  
 TITLE: Analysis of prostaglandin G/H synthase-2 inhibition using peroxidase-induced luminol luminescence.  
 AUTHOR: Forghani F; Ouellet M; Keen S; Percival M D; Tagari P  
 CORPORATE SOURCE: Merck Frosst Centre for Therapeutic Research, Pointe Claire-Dorval, Quebec, Canada.  
 SOURCE: Analytical biochemistry, (1998 Nov 15) Vol. 264, No. 2, pp. 216-21.  
 Journal code: 0370535. ISSN: 0003-2697.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199902  
 ENTRY DATE: Entered STN: 1 Mar 1999  
 Last Updated on STN: 1 Mar 1999  
 Entered Medline: 12 Feb 1999

ED Entered STN: 1 Mar 1999  
 Last Updated on STN: 1 Mar 1999  
 Entered Medline: 12 Feb 1999

AB The inducible form of the heme-protein prostaglandin G/H synthase (PGHS-2 or COX-2) has been established as a pivotal enzyme in the cascade of events leading to inflammation, hyperalgesia, and pyresis and represents a major therapeutic target in inflammatory disease. Accordingly, we have exploited the heme-catalyzed hydroperoxidase activity of recombinant hCOX-2 to generate luminescence in the presence of luminol, or a cyclic naphthalene hydrazide,

and the substrate arachidonic acid. Arachidonate-induced luminescence was shown to be an index of real-time catalytic activity and demonstrated the turnover inactivation of the enzyme. Luminol luminescence was proportional to hCOX-2 concentration and gave accurate  $K_m$  determinations for arachidonate. Inhibition of hCOX-2 activity, measured by luminescence, by a variety of selective (for COX-2) and nonselective inhibitors showed rank orders of potency similar to those observed with other in vitro and whole cell methods using the recombinant protein. The sensitivity of the luminescence assay also allowed determination of inhibitor potency at substrate concentrations below  $K_m$ , distinguishing competitive inhibitors such as ibuprofen from time-dependent inhibitors such as DuP-697. Finally the use of higher quantum-yielding luminol analogues allowed measurement of cyclooxygenase activity at extremely low substrate and protein concentrations, enabling a variety of novel assay formats.

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ACCESSION NUMBER: 2005536242 EMBASE Full-text  
 TITLE: Mild and practical method for the  $\alpha$ -arylation of nitriles with heteroaryl halides.  
 AUTHOR: Klapars A.; Waldman J.H.; Campos K.R.; Jensen M.S.; McLaughlin M.; Chung J.Y.L.; Cvetovich R.J.; Chen C.-Y.  
 CORPORATE SOURCE: A. Klapars, Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, United States. [artis\\_klapars@merck.com](mailto:artis_klapars@merck.com)  
 SOURCE: Journal of Organic Chemistry, (25 Nov 2005) Vol. 70, No. 24, pp. 10186-10189. .  
 Refs: 22  
 ISSN: 0022-3263 CODEN: JOCEAH  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 029 Clinical Biochemistry  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 29 Dec 2005  
 Last Updated on STN: 29 Dec 2005

ED Entered STN: 29 Dec 2005

Last Updated on STN: 29 Dec 2005

AB A mild and transition-metal-free method for the  $\alpha$ -arylation of aliphatic nitriles with activated heteroaryl halides was developed using NaHMDS or KHMDS as base at ambient temperature. The key to the success of this method is generation of the nitrile anion in the presence of the heteroaryl halide. The method is applicable to both primary and secondary carbonitriles and a wide range of heteroaryl halides. Selective monoarylation was observed with primary carbonitriles. The operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative to the preparation of  $\alpha$ -heteroaryl carbonitriles. .COPYRGHT. 2005 American Chemical Society.

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ACCESSION NUMBER: 2005504604 EMBASE Full-text  
 TITLE: P38 MAP kinase inhibitors: Evolution of imidazole-based and pyrido-pyrimidin-2-one lead classes.  
 AUTHOR: Natarajan S.R.; Doherty J.B.  
 CORPORATE SOURCE: S.R. Natarajan, Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway,

SOURCE: NJ 07065, United States. ravi\_natarajan@merck.com  
 Current Topics in Medicinal Chemistry, (2005) Vol. 5, No. 10, pp. 987-1003. .  
 Refs: 25  
 ISSN: 1568-0266 CODEN: CTMCCL  
 COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 030 Pharmacology  
 031 Arthritis and Rheumatism  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 28 Nov 2005  
 Last Updated on STN: 28 Nov 2005  
 ED Entered STN: 28 Nov 2005  
 Last Updated on STN: 28 Nov 2005  
 AB The initial disclosure of tri-substituted imidazole-based drug molecules such as 1 for inhibition of p38 MAP kinase by SmithKline Beecham (SB) sparked an effort in this area at Merck and other pharmaceutical research establishments. Although analogs in this class have shown good inhibitory properties against p38 MAP kinase, their selectivity profile were modest and left much room for improvement. Attempts to discover newer compounds with improved selectivity over the prototypical SB compound 203580 (1), led to the discovery of a new sub-class of p38 inhibitors typified by compound 18 at Merck. Although this benchmark compound was potent, highly selective and orally efficacious it was burdened with compound related adverse effects in dogs that has delayed further development. In 1999, a new class of p38 inhibitors represented by clinical candidate VX-745 (26), was disclosed by Vertex Pharmaceuticals. This compound displayed unprecedented selectivity due to its unique mode of binding to the active site in p38 MAP kinase. Inspired by the exquisite selectivity profile of VX-745 [26] a scaffold re-design was initiated at Merck which resulted in the discovery of the quinazolinone, pyrimido-pyrimidone, pyrido-pyrimidone, quinolinone and naphthyridinone based p38 inhibitors. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L100 ANSWER 8 OF 9 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
 ACCESSION NUMBER: 2002293083 EMBASE Full-text  
 TITLE: Pharmacological characterization of a novel cell line expressing human  $\alpha(4)\beta(3)\delta$  GABA(A) receptors.  
 AUTHOR: Brown N.; Kerby J.; Bonnert T.P.; Whiting P.J.; Wafford K.A.  
 CORPORATE SOURCE: K.A. Wafford, Merck Sharp and Dohme Res. Lab., Neuroscience Research Centre, Eastwick Road, Harlow, Essex CM20 2QR, United Kingdom. keith\_wafford@merck.com  
 SOURCE: British Journal of Pharmacology, (2002) Vol. 136, No. 7, pp. 965-974. .  
 Refs: 38  
 ISSN: 0007-1188 CODEN: BJPCBM  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 002 Physiology  
 008 Neurology and Neurosurgery  
 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 5 Sep 2002

Last Updated on STN: 5 Sep 2002

ED Entered STN: 5 Sep 2002

Last Updated on STN: 5 Sep 2002

AB 1. The pharmacology of the stable cell line expressing human  $\alpha(4)\beta(3)\delta$  GABA(A) receptor was investigated using whole-cell patch-clamp techniques. 2.  $\alpha(4)\beta(3)\delta$  receptors exhibited increased sensitivity to GABA when compared to  $\alpha(4)\beta(3)\gamma(2)$  receptors, with EC(50)'s of 0.50 (0.46, 0.53)  $\mu$ M and 2.6 (2.5, 2.6)  $\mu$ M respectively. Additionally, the GABA partial agonists piperidine-4-sulphonate (P4S) and 4,5,6,7-tetrahydroisothiazolo-[5,4-c]pyridin-3-ol (THIP) displayed markedly higher efficacy at  $\alpha(4)\beta(3)\delta$  receptors, indeed THIP demonstrated greater efficacy than GABA at these receptors. 3. The  $\delta$  subunit conferred slow desensitization to GABA, with rate constants of  $4.8 \pm 0.5$  s for  $\alpha(4)\beta(3)\delta$  and  $2.5 \pm 0.2$  s for  $\alpha(4)\beta(3)\gamma(2)$ . However, both P4S and THIP demonstrated similar levels of desensitization on both receptor subtypes suggesting this effect is agonist specific. 4.  $\alpha(4)\beta(3)\delta$  and  $\alpha(4)\beta(3)\gamma(2)$  demonstrated equal sensitivity to inhibition by the cation zinc (2-3  $\mu$ M IC(50)). However,  $\alpha(4)\beta(3)\delta$  receptors demonstrated greater sensitivity to inhibition by lanthanum. The IC(50) for GABA antagonists SR-95531 and picrotoxin, was similar for  $\alpha(4)\beta(3)\delta$  and  $\alpha(4)\beta(3)\gamma(2)$ . Likewise, inhibition was observed on both subtypes at high and low pH. 5.  $\alpha(4)\beta(3)\delta$  receptors were insensitive to modulation by benzodiazepine ligands. In contrast Ro15-4513 and bretazenil potentiated GABA responses on  $\alpha(4)\beta(3)\gamma(2)$  cells, and the inverse agonist DMCM showed allosteric inhibition of  $\alpha(4)\beta(3)\gamma(2)$  receptors. 6. The efficacy of neurosteroids at  $\alpha(4)\beta(3)\delta$  receptors was greatly enhanced over that observed at  $\alpha(4)\beta(3)\gamma(2)$  receptors. The greatest effect was observed using THDOC with  $524 \pm 71.6\%$  potentiation at  $\alpha(4)\beta(3)\delta$  and  $297.9 \pm 49.7\%$  at  $\alpha(4)\beta(3)\gamma(2)$  receptors. Inhibition by the steroid pregnenolone sulphate however, showed no subtype selectivity. The efficacy of both pentobarbitone and propofol was slightly augmented and etomidate greatly enhanced at  $\alpha(4)\beta(3)\delta$  receptors versus  $\alpha(4)\beta(3)\gamma(2)$  receptors. 7. We show that the  $\alpha(4)\beta(3)\delta$  receptor has a distinct pharmacology and kinetic profile. With its restricted distribution within the brain and unique pharmacology this receptor may play an important role in the action of neurosteroids and anaesthetics.

L100 ANSWER 9 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 ACCESSION NUMBER: 1989:185257 BIOSIS Full-text  
 DOCUMENT NUMBER: PREV198987096523; BA87:96523  
 TITLE: SYNTHESIS OF THYROID HORMONE ANALOGUES PART 1. PREPARATION OF 3' HETEROARYLMETHYL-3 5-DIIODO-L-THYRONINES VIA PHENOL-DINITROPHENOL CONDENSATION AND RELATIONSHIPS BETWEEN STRUCTURE AND SELECTIVE THYROMIMETIC ACTIVITY.  
 AUTHOR(S): LEESON P D [Reprint author]; EMMETT J C  
 CORPORATE SOURCE: **MERCK** SHARP DOHME RES LAB, NEUROSCI RES CENT, TERLINGS PARK, EASTWICK ROAD, HARLOW, ESSEX, CM20 2QR, UK  
 SOURCE: Journal of the Chemical Society Perkin Transactions I, (1988) No. 12, pp. 3085-3096.  
 CODEN: JCPRB4. ISSN: 0300-922X.  
 DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH  
 ENTRY DATE: Entered STN: 9 Apr 1989  
 Last Updated on STN: 20 Jun 1989  
 ED Entered STN: 9 Apr 1989  
 Last Updated on STN: 20 Jun 1989

AB 3'-Heteroarylmethyl analogues (1)-(8) of the natural thyroid hormone 3,3',5-tri-iodo-L-thyronine (T3) were synthesized as potential selective (cardiac-sparing) thyromimetics. The diphenyl ether moiety was constructed by condensation of 3-substituted 4-methoxyphenols with a 3,5-dinitro-L-tyrosine derivative. Synthesis of the key phenols (28)-(32) required the in situ preparation, at low temperatures, of the novel metallated species 2-lithio-5-methoxypyridine (14), 5-lithio-2-methoxypyrimidine (15), 5-lithio-2-methylpyridine (16), 5-bromo-4-lithio-2-methoxypyridine (18), and 2,6-difluoro-3-lithiopyridine (19), followed by reaction with the benzaldehyde (20). Alternative routes to the pyridazinone (36) and thiazolone (37) phenols were developed from the benzyl bromide (33). Structure-activity relationships indicate that selective thyromimetic activity is associated with 2-oxyheteroaren-5-ylmethyl 3'-substitution, as found in the pyridone (1), pyridazinone (2), hydroxypyridine (4) and thiazolone (8). The location of the oxy substituent in the heterocycle is critical for both hormonal activity and for binding to the T3 receptor.

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 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.  
 LAST RELOADED: Dec 19, 2006 (20061219/UP).

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(FILE 'HOME' ENTERED AT 11:10:44 ON 20 DEC 2006)

FILE 'ZCAPLUS' ENTERED AT 11:11:04 ON 20 DEC 2006  
 E US2004-518503/APPS

L1 FILE 'HCAPLUS' ENTERED AT 11:12:26 ON 20 DEC 2006  
 1 SEA ABB=ON PLU=ON US2004-518503/APPS  
 SAVE TEMP L1 JAI503HCAAPP/A

FILE 'STNGUIDE' ENTERED AT 11:12:57 ON 20 DEC 2006  
 D QUE

FILE 'HCAPLUS' ENTERED AT 11:13:35 ON 20 DEC 2006  
 D IBIB ED AB IND

FILE 'STNGUIDE' ENTERED AT 11:13:41 ON 20 DEC 2006

L2 FILE 'WPIX' ENTERED AT 11:14:28 ON 20 DEC 2006  
 1 SEA ABB=ON PLU=ON US2004-518503/APPS  
 SAVE TEMP L2 JAI503WPIAPP/A

FILE 'STNGUIDE' ENTERED AT 11:14:52 ON 20 DEC 2006  
 D QUE

FILE 'WPIX' ENTERED AT 11:15:06 ON 20 DEC 2006  
 D IALL CODE L2

FILE 'STNGUIDE' ENTERED AT 11:15:09 ON 20 DEC 2006

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FILE 'REGISTRY' ENTERED AT 11:16:01 ON 20 DEC 2006

L3 FILE 'HCAPLUS' ENTERED AT 11:16:10 ON 20 DEC 2006  
TRA PLU=ON L1 1- RN : 35 TERMS

L4 FILE 'REGISTRY' ENTERED AT 11:16:12 ON 20 DEC 2006  
35 SEA ABB=ON PLU=ON L3  
SAVE TEMP L4 JAI503REGAPP/A  
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:16:52 ON 20 DEC 2006

L5 FILE 'LREGISTRY' ENTERED AT 11:18:51 ON 20 DEC 2006  
STR

L6 FILE 'REGISTRY' ENTERED AT 11:21:25 ON 20 DEC 2006  
1 SEA SSS SAM L5  
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:22:09 ON 20 DEC 2006  
D QUE STAT

L7 FILE 'REGISTRY' ENTERED AT 11:23:52 ON 20 DEC 2006  
D QUE STAT  
21 SEA SSS FUL L5  
SAVE TEMP L7 JAI503PSET1/A

L8 ANALYZE PLU=ON L7 1- LC : 4 TERMS  
D 1-

L9 FILE 'LREGISTRY' ENTERED AT 11:25:10 ON 20 DEC 2006  
STR L5

L10 FILE 'REGISTRY' ENTERED AT 11:25:45 ON 20 DEC 2006  
1 SEA SSS SAM L9  
D QUE STAT

FILE 'STNGUIDE' ENTERED AT 11:26:51 ON 20 DEC 2006

L11 FILE 'LREGISTRY' ENTERED AT 11:34:30 ON 20 DEC 2006  
STR L9

L12 FILE 'REGISTRY' ENTERED AT 11:35:45 ON 20 DEC 2006  
35 SEA SSS SAM L11

L13 FILE 'LREGISTRY' ENTERED AT 11:36:15 ON 20 DEC 2006  
STR L11

L14 FILE 'REGISTRY' ENTERED AT 11:36:48 ON 20 DEC 2006  
4 SEA SSS SAM L13  
D SCAN  
D QUE STAT

L15 85 SEA SSS FUL L13  
SAVE TEMP L15 JAI503PSET2/A

L16 ANALYZE PLU=ON L15 1- LC : 7 TERMS  
D 1-

FILE 'STNGUIDE' ENTERED AT 11:39:33 ON 20 DEC 2006

L17 FILE 'ZCAPLUS' ENTERED AT 11:40:35 ON 20 DEC 2006  
QUE ABB=ON PLU=ON EGGENWEILER, H?/AU

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L18 QUE ABB=ON PLU=ON WOLF, M?/AU  
L19 QUE ABB=ON PLU=ON MERCK/PA,CS,SO  
L20 QUE ABB=ON PLU=ON (WOLF OR EGGENWEILER)/AU  
L21 QUE ABB=ON PLU=ON AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004  
OR REVIEW/DT  
L22 QUE ABB=ON PLU=ON AY<2004 OR PY<2004 OR PRY<2004

FILE 'REGISTRY' ENTERED AT 11:42:50 ON 20 DEC 2006  
L23 3 SEA ABB=ON PLU=ON L15 AND CASREACT/LC

FILE 'STNGUIDE' ENTERED AT 11:43:06 ON 20 DEC 2006

FILE 'ZCAPLUS' ENTERED AT 11:43:35 ON 20 DEC 2006  
L24 QUE ABB=ON PLU=ON ?PHOSPHODIESTERAS? OR (?PHOSPHO(W)DIESTERAS  
?) OR (?PHOSPHODI(W)ESTERAS?)

FILE 'REGISTRY' ENTERED AT 11:44:37 ON 20 DEC 2006  
L25 14 SEA ABB=ON PLU=ON L4 NOT L15  
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:44:55 ON 20 DEC 2006

FILE 'REGISTRY' ENTERED AT 11:46:06 ON 20 DEC 2006  
L26 21 SEA ABB=ON PLU=ON L15 AND L4

FILE 'STNGUIDE' ENTERED AT 11:46:35 ON 20 DEC 2006

FILE 'ZCAPLUS' ENTERED AT 11:46:38 ON 20 DEC 2006  
L27 QUE ABB=ON PLU=ON ?PYRIDAZIN?  
L28 QUE ABB=ON PLU=ON ?THIAZOL? OR ?THIOPHEN?  
D SAVED

FILE 'HCAPLUS' ENTERED AT 11:49:00 ON 20 DEC 2006  
L29 1 SEA ABB=ON PLU=ON L7  
L30 32 SEA ABB=ON PLU=ON L15  
L31 32 SEA ABB=ON PLU=ON (L29 OR L30)  
L32 31 SEA ABB=ON PLU=ON L31 AND (L24 OR L27 OR L28)  
L33 32 SEA ABB=ON PLU=ON L31 OR L32  
L34 31 SEA ABB=ON PLU=ON L33 AND L21  
L35 32 SEA ABB=ON PLU=ON (L33 OR L34)  
SAVE TEMP L35 JAI503HCAB/A  
L36 3 SEA ABB=ON PLU=ON L31 AND (L17 OR L18 OR L19)  
D SCAN TI HIT  
SAVE TEMP L36 JAI503HCAINV/A

FILE 'USPATFULL, USPAT2' ENTERED AT 11:51:32 ON 20 DEC 2006  
L37 1 SEA ABB=ON PLU=ON L7  
L38 42 SEA ABB=ON PLU=ON L15  
L39 42 SEA ABB=ON PLU=ON (L37 OR L38)  
L40 1 SEA ABB=ON PLU=ON L39 AND L24/TI, IT, CC, CT, ST, STP, BI, AB  
L41 36 SEA ABB=ON PLU=ON L39 AND A61?/IPC  
L42 1 SEA ABB=ON PLU=ON L41 AND A61P?/IPC  
L43 2 SEA ABB=ON PLU=ON L37 OR L40 OR L42  
SAVE TEMP L43 JAI503USP1B/A  
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:54:12 ON 20 DEC 2006

FILE 'TOXCENTER' ENTERED AT 11:54:29 ON 20 DEC 2006  
L44 1 SEA ABB=ON PLU=ON L7

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L45 6 SEA ABB=ON PLU=ON L15  
L46 6 SEA ABB=ON PLU=ON (L44 OR L45)  
SAVE TEMP L46 JAI503TOXB/A  
L47 1 SEA ABB=ON PLU=ON L46 AND (L17 OR L18 OR L19)  
SAVE TEMP L47 JAI503TOXINV/A

FILE 'CASREACT' ENTERED AT 11:55:28 ON 20 DEC 2006  
L48 3 SEA ABB=ON PLU=ON L23  
SAVE TEMP L48 JAI503CRXB/A

FILE 'STNGUIDE' ENTERED AT 11:56:11 ON 20 DEC 2006  
D SAVED

FILE 'BEILSTEIN' ENTERED AT 11:56:55 ON 20 DEC 2006  
D QUE L15  
L49 17 SEA SSS FUL L13  
SAVE TEMP L49 JAI503BEIP/A  
L50 1 SEA ABB=ON PLU=ON L49 NOT BABSAN/FA  
SELECT L49 1- BABSAN

FILE 'BABS' ENTERED AT 11:58:18 ON 20 DEC 2006  
L51 6 SEA ABB=ON PLU=ON (5596494/AN OR 6388164/AN OR 5856247/AN OR  
6347066/AN OR 6428743/AN OR 6531693/AN)  
SAVE TEMP L51 JAI503BAB/A

FILE 'CHEMINFORMRX' ENTERED AT 11:58:59 ON 20 DEC 2006  
D QUE L15  
L52 0 SEA SSS SAM L13 ( 0 REACTIONS)  
L53 2 SEA SSS FUL L13 ( 6 REACTIONS)  
SAVE TEMP L53 JAI503CHMP/A  
D SCAN

FILE 'STNGUIDE' ENTERED AT 12:00:07 ON 20 DEC 2006  
D SAVED

FILE 'WPIX' ENTERED AT 12:00:45 ON 20 DEC 2006  
D QUE L15  
L54 2 SEA SSS SAM L13  
L55 35 SEA SSS FUL L13  
SAVE TEMP L55 JAI503WPIS/A  
SELECT L55 1- SDCN  
L56 11 SEA ABB=ON PLU=ON (RACQNP/DCN OR RACVZA/DCN OR RACVZB/DCN OR  
RACVZC/DCN OR RACVZD/DCN OR RACVZE/DCN OR RACVZF/DCN OR  
RACVZG/DCN OR RACVZH/DCN OR RACVZI/DCN OR RACVZM/DCN OR  
RACVZN/DCN OR RACVZO/DCN OR RACVZP/DCN OR RACVZ3/DCN OR  
RACVZ4/DCN OR RACVZ5/DCN OR RACVZ6/DCN OR RACVZ7/DCN OR  
RACVZ8/DCN OR RACVZ9/DCN OR RANV5C/DCN OR RANV5G/DCN OR  
RANV5P/DCN OR RANV5Q/DCN OR RANV6F/DCN OR RANV66/DCN OR  
RA1KDF/DCN OR RA1RZ6/DCN OR RA4W3Q/DCN OR RA4XH0/DCN OR  
RA4X3I/DCN OR RA4X4A/DCN OR RA4X4D/DCN OR RA6SZ8/DCN)  
L57 11 SEA ABB=ON PLU=ON L55/DCR  
L58 11 SEA ABB=ON PLU=ON (L56 OR L57)  
SAVE TEMP L58 JAI503WPIB/A  
L59 QUE ABB=ON PLU=ON F530/M0,M1,M2,M3,M4,M5,M6  
L60 4 SEA ABB=ON PLU=ON L58 NOT L59  
D TRI 1-4  
L61 635 SEA ABB=ON PLU=ON (L58 OR L59) AND (L17 OR L18 OR L19)  
L62 1 SEA ABB=ON PLU=ON L61 AND L58  
SAVE TEMP L62 JAI503WPIINV/A

FILE 'STNGUIDE' ENTERED AT 12:04:41 ON 20 DEC 2006  
D SAVED

FILE 'WPIX' ENTERED AT 12:05:16 ON 20 DEC 2006

L63 10 SEA ABB=ON PLU=ON L58 NOT (L17 OR L18 OR L19)  
L64 9 SEA ABB=ON PLU=ON L63 AND L22  
D TRI 1-9

FILE 'STNGUIDE' ENTERED AT 12:06:29 ON 20 DEC 2006

FILE 'REGISTRY' ENTERED AT 12:07:20 ON 20 DEC 2006  
SELECT L7 1- CN  
D SELECT

FILE 'STNGUIDE' ENTERED AT 12:08:01 ON 20 DEC 2006

FILE 'MEDLINE' ENTERED AT 12:08:05 ON 20 DEC 2006

E PYRIDAZIN/CT  
L65 QUE ABB=ON PLU=ON PYRIDAZINES+PFT,OLD,NEW,NT/CT  
E THIOPHENE/CT  
L66 QUE ABB=ON PLU=ON THIOPHENES+PFT,OLD,NEW,NT/CT  
E THIAZOLES/CT  
L67 QUE ABB=ON PLU=ON THIAZOLES+PFT,OLD,NEW,NT/CT  
L68 257 SEA ABB=ON PLU=ON L65 AND (L66 OR L67 OR L28)  
E PHOSPHODIESTERASE/CT  
E E148+ALL  
L69 QUE ABB=ON PLU=ON "PHOSPHODIESTERASE INHIBITORS"+PFT,OLD,NEW,  
NT/CT  
L70 QUE ABB=ON PLU=ON "PHOSPHODIESTERASES/ANTAGONISTS & INHIBITOR  
S"+PFT,OLD,NEW,NT/CT  
L71 11 SEA ABB=ON PLU=ON L68 AND (L24 OR (L69 OR L70))  
SAVE TEMP L71 JAI503MED1B/A  
D TRI 5-10  
L72 2 SEA ABB=ON PLU=ON L68 AND (L17 OR L18 OR L19)  
SAVE TEMP L72 JAI503MEDINV/A

FILE 'EMBASE' ENTERED AT 12:12:28 ON 20 DEC 2006

E PYRIDAZIN/CT  
E PYRIDAZINE/CT  
L\*\*\* DEL QUE "PYRIDAZINE DERIVATIVE"  
L73 QUE ABB=ON PLU=ON "PYRIDAZINE DERIVATIVE"+PFT,OLD,NEW,NT/CT  
E PYRIDAZINONE/CT  
L74 QUE ABB=ON PLU=ON "PYRIDAZINONE DERIVATIVE"+PFT,OLD,NEW,NT/CT  
  
E THIAZOLE/CT  
E THIAZOLE DERIVATIVE/CT

FILE 'STNGUIDE' ENTERED AT 12:14:14 ON 20 DEC 2006

FILE 'EMBASE' ENTERED AT 12:19:01 ON 20 DEC 2006

L75 QUE ABB=ON PLU=ON "THIAZOLE DERIVATIVE"+PFT,OLD,NEW,NT/CT  
E THIOPHENE/CT  
E THIOPHENE DERIV/CT  
L76 QUE ABB=ON PLU=ON "THIOPHENE DERIVATIVE"+PFT,OLD,NEW,NT/CT  
L77 217 SEA ABB=ON PLU=ON (L73 OR L74) AND ((L75 OR L76) OR L28)  
E PHOSPHODIESTERASE/CT  
E PHOSPHODIESTERASE INHIBITOR/CT  
L78 QUE ABB=ON PLU=ON "PHOSPHODIESTERASE INHIBITOR"+PFT,OLD,NEW,N  
T/CT  
L79 102 SEA ABB=ON PLU=ON L77 AND L78

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L80 67 SEA ABB=ON PLU=ON L79/MAJ  
L81 59 SEA ABB=ON PLU=ON L80 AND L21  
L82 41 SEA ABB=ON PLU=ON L81 AND (L75 OR L76)  
D TRI 30-35  
L83 49 SEA ABB=ON PLU=ON L27(5A)L28  
L84 0 SEA ABB=ON PLU=ON L83 AND L78  
L85 14 SEA ABB=ON PLU=ON L77 AND L83  
L86 0 SEA ABB=ON PLU=ON L83 AND L24  
L87 14 SEA ABB=ON PLU=ON (L84 OR L85 OR L86)  
SAVE TEMP L87 JAI503EMBB/A  
L88 3 SEA ABB=ON PLU=ON L77 AND (L17 OR L18 OR L19)  
SAVE TEMP L88 JAI503EMBINV/A

FILE 'STNGUIDE' ENTERED AT 12:24:37 ON 20 DEC 2006  
D SAVED

FILE 'BIOSIS, PASCAL, JICST-EPLUS, JAPIO, LIFESCI, BIOENG, BIOTECHNO,  
BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI, DISSABS' ENTERED  
AT 12:26:38 ON 20 DEC 2006

L89 348 SEA ABB=ON PLU=ON L27(5A) L28  
L90 0 SEA ABB=ON PLU=ON L89 AND L24  
L91 423 SEA ABB=ON PLU=ON L27(7A) L28  
L92 1 SEA ABB=ON PLU=ON L91 AND L24  
D SCAN  
D TRI  
SAVE TEMP L92 JAI503MULB/A  
L93 1 SEA ABB=ON PLU=ON L91 AND (L19 OR L20)  
SAVE TEMP L93 JAI503MULINV/A  
D SAVED

FILE 'STNGUIDE' ENTERED AT 12:30:50 ON 20 DEC 2006

FILE 'MARPAT' ENTERED AT 12:31:08 ON 20 DEC 2006

D QUE L15  
L94 3 SEA SSS SAM L13  
D QUE STAT  
L95 57 SEA SSS FUL L13  
SAVE TEMP L95 JAI503MARPA/A

FILE 'LREGISTRY' ENTERED AT 12:32:07 ON 20 DEC 2006

D QUE L7  
L96 STR L9

FILE 'MARPAT' ENTERED AT 12:35:04 ON 20 DEC 2006

L97 0 SEA SUB=L95 SSS SAM L96  
D QUE STAT  
L98 2 SEA SUB=L95 SSS FUL L96  
SAVE TEMP L98 JAI503MARR/A  
D SCAN

FILE 'STNGUIDE' ENTERED AT 12:36:32 ON 20 DEC 2006

D SAVED  
D QUE STAT L7  
D QUE NOS L8  
D L8 1-  
D QUE STAT L15  
D QUE NOS L16  
D L16 1-  
D QUE L35  
D QUE NOS L43

D QUE NOS L46  
 D QUE NOS L48  
 D QUE STAT L49  
 D QUE L51  
 D QUE STAT L53  
 D QUE STAT L55  
 D QUE NOS L58  
 D QUE STAT L95  
 D QUE STAT L98  
 D QUE L71  
 D QUE L87  
 D QUE L92

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CASREACT, BABS, CHEMINFORMRX, WPIX,  
 MARPAT, MEDLINE, EMBASE, DRUGU' ENTERED AT 12:42:22 ON 20 DEC 2006  
 L99 69 DUP REM L35 L43 L46 L48 L51 L53 L58 L98 L71 L87... (21 DUPLI  
 ANSWERS '1-32' FROM FILE HCAPLUS  
 ANSWERS '33-34' FROM FILE USPATFULL  
 ANSWER '35' FROM FILE TOXCENTER  
 ANSWERS '36-37' FROM FILE CHEMINFORMRX  
 ANSWERS '38-42' FROM FILE WPIX  
 ANSWER '43' FROM FILE MARPAT  
 ANSWERS '44-54' FROM FILE MEDLINE  
 ANSWERS '55-68' FROM FILE EMBASE  
 ANSWER '69' FROM FILE DRUGU

FILE 'STNGUIDE' ENTERED AT 12:42:35 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
 DRUGU, MARPAT' ENTERED AT 12:43:22 ON 20 DEC 2006  
 D IBIB ED AB HITIND RETABLE HITSTR

FILE 'STNGUIDE' ENTERED AT 12:43:30 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
 DRUGU, MARPAT' ENTERED AT 12:44:12 ON 20 DEC 2006  
 D IBIB ED AB HITIND RETABLE HITSTR 2-32

FILE 'STNGUIDE' ENTERED AT 12:45:14 ON 20 DEC 2006

FILE 'BEILSTEIN' ENTERED AT 12:45:58 ON 20 DEC 2006  
 D L50 IDE

FILE 'STNGUIDE' ENTERED AT 12:45:59 ON 20 DEC 2006

FILE 'BEILSTEIN' ENTERED AT 12:46:08 ON 20 DEC 2006  
 D L50 RX

FILE 'STNGUIDE' ENTERED AT 12:46:10 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
 DRUGU, MARPAT' ENTERED AT 12:46:26 ON 20 DEC 2006  
 D IBIB AB HITSTR 33-34

FILE 'STNGUIDE' ENTERED AT 12:46:28 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
 DRUGU, MARPAT' ENTERED AT 12:46:42 ON 20 DEC 2006  
 D IBIB ED AB HITIND 35

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FILE 'STNGUIDE' ENTERED AT 12:46:43 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
DRUGU, MARPAT' ENTERED AT 12:46:58 ON 20 DEC 2006  
D IBIB ED AB HIT 36

FILE 'STNGUIDE' ENTERED AT 12:47:05 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
DRUGU, MARPAT' ENTERED AT 12:47:16 ON 20 DEC 2006  
D BIB AB HIT 37

FILE 'STNGUIDE' ENTERED AT 12:47:18 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
DRUGU, MARPAT' ENTERED AT 12:47:36 ON 20 DEC 2006  
D IALL ABEQ TECH ABEX HITSTR 38-42

FILE 'STNGUIDE' ENTERED AT 12:47:45 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
DRUGU, MARPAT' ENTERED AT 12:48:15 ON 20 DEC 2006  
D IBIB AB FHIT 43

FILE 'STNGUIDE' ENTERED AT 12:48:16 ON 20 DEC 2006

FILE 'HCAPLUS, USPATFULL, TOXCENTER, CHEMINFORMRX, WPIX, MEDLINE, EMBASE,  
DRUGU, MARPAT' ENTERED AT 12:49:15 ON 20 DEC 2006  
D IBIB ED AB IND 44-69

FILE 'STNGUIDE' ENTERED AT 12:49:17 ON 20 DEC 2006

D QUE NOS L36  
D QUE NOS L47  
D QUE NOS L62  
D QUE L72  
D QUE L88  
D QUE L93

FILE 'HCAPLUS, TOXCENTER, WPIX, MEDLINE, EMBASE, BIOSIS' ENTERED AT  
12:51:07 ON 20 DEC 2006

L100 9 DUP REM L36 L47 L62 L72 L88 L93 (2 DUPLICATES REMOVED)  
ANSWERS '1-3' FROM FILE HCAPLUS  
ANSWERS '4-5' FROM FILE MEDLINE  
ANSWERS '6-8' FROM FILE EMBASE  
ANSWER '9' FROM FILE BIOSIS

FILE 'STNGUIDE' ENTERED AT 12:51:14 ON 20 DEC 2006

FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 12:51:22 ON 20 DEC 2006  
D IBIB ED AB 1-9

FILE 'STNGUIDE' ENTERED AT 12:51:23 ON 20 DEC 2006

FILE 'STNGUIDE' ENTERED AT 12:51:32 ON 20 DEC 2006

FILE HOME

FILE ZCAPLUS

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FILE LAST UPDATED: 19 Dec 2006 (20061219/ED)

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FILE STNGUIDE  
FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Dec 19, 2006 (20061219/UP).

FILE WPIX  
FILE LAST UPDATED: 18 DEC 2006 <20061218/UP>  
MOST RECENT THOMSON SCIENTIFIC UPDATE: 200681 <200681/DW>  
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[http://www.stn-international.de/stndatabases/details/ipc\\_reform.html](http://www.stn-international.de/stndatabases/details/ipc_reform.html) and  
<http://scientific.thomson.com/media/scpdf/ipcrdwpf.pdf>

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PLEASE SEE  
[http://www.stn-international.de/stndatabases/details/dwpi\\_r.html](http://www.stn-international.de/stndatabases/details/dwpi_r.html) <<<

# FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 19 DEC 2006 HIGHEST RN 916029-54-4

DICTIONARY FILE UPDATES: 19 DEC 2006 HIGHEST RN 916029-54-4

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TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

# FILE LREGISTRY

LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

# FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 19 Dec 2006 (20061219/PD)

FILE LAST UPDATED: 19 Dec 2006 (20061219/ED)

HIGHEST GRANTED PATENT NUMBER: US7152245

HIGHEST APPLICATION PUBLICATION NUMBER: US2006282930

CA INDEXING IS CURRENT THROUGH 19 Dec 2006 (20061219/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 19 Dec 2006 (20061219/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

# FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 19 Dec 2006 (20061219/PD)

FILE LAST UPDATED: 19 Dec 2006 (20061219/ED)

HIGHEST GRANTED PATENT NUMBER: US2006182892

HIGHEST APPLICATION PUBLICATION NUMBER: US2006282212

CA INDEXING IS CURRENT THROUGH 19 Dec 2006 (20061219/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 19 Dec 2006 (20061219/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

# FILE TOXCENTER

FILE COVERS 1907 TO 19 Dec 2006 (20061219/ED)

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2007 vocabulary.

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* CASREACT now has more than 10 million reactions
*
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Some CASREACT records are derived from the ZIC/VINITI database (1974-1991) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE LAST UPDATED ON JUNE 16, 2006

**FILE CONTAINS 9,606,495 SUBSTANCES**

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For more detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

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```
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
```

**NEW**

\* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE  
SEARCHED, SELECTED AND TRANSFERRED.

\* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES,  
ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A  
COMPOUND AT A GLANCE.

## FILE BABS

FILE LAST UPDATED: 25 SEP 2006 <20060925/UP>  
FILE COVERS 1980 TO DATE.

## FILE CHEMINFORMRX

FILE LAST UPDATED: 5 DEC 2006 <20061205/UP>

>>> CAS Registry Numbers are available for  
substances prior to 1995 <<<

## FILE MEDLINE

FILE LAST UPDATED: 19 Dec 2006 (20061219/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been  
added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))  
and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

## FILE EMBASE

FILE COVERS 1974 TO 20 Dec 2006 (20061220/ED)

EMBASE is now updated daily. SDI frequency remains weekly (default)  
and biweekly.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

## FILE BIOSIS

FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 14 December 2006 (20061214/ED)

## FILE PASCAL

FILE LAST UPDATED: 18 DEC 2006 <20061218/UP>  
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE  
IN THE BASIC INDEX (/BI) FIELD <<<

## FILE JICST-EPLUS

FILE COVERS 1985 TO 18 DEC 2006 (20061218/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED  
TERM (/CT) THESAURUS RELOAD.

## FILE JAPIO

FILE LAST UPDATED: 12 DEC 2006 <20061212/UP>

FILE COVERS APRIL 1973 TO AUGUST 31, 2006

>>> GRAPHIC IMAGES AVAILABLE <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN FILE JAPIO.

SEE HELP CHANGE

AND

[http://www.stn-international.de/stndatabases/details/ipc\\_reform.html](http://www.stn-international.de/stndatabases/details/ipc_reform.html) <<<

FILE LIFESCI

FILE COVERS 1978 TO 10 Nov 2006 (20061110/ED)

FILE BIOENG

FILE LAST UPDATED: 20 NOV 2006 <20061120/UP>

FILE COVERS 1982 TO DATE

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN  
THE BASIC INDEX <<<

FILE BIOTECHNO

FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>

FILE COVERS 1980 TO 2003.

>>> BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004 <<<

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN  
/CT AND BASIC INDEX <<<

FILE BIOTECHDS

FILE LAST UPDATED: 13 DEC 2006 <20061213/UP>

FILE COVERS 1982 TO DATE

>>> USE OF THIS FILE IS LIMITED TO BIOTECH SUBSCRIBERS <<<

FILE DRUGU

FILE LAST UPDATED: 19 DEC 2006 <20061219/UP>

>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<

>>> THESAURUS AVAILABLE IN /CT <<<

FILE DRUGB

>>> FILE COVERS 1964 TO 1982 - CLOSED FILE <<<

FILE VETU

FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>

FILE COVERS 1983-2001

FILE VETB

FILE LAST UPDATED: 25 SEP 94 <940925/UP>

FILE COVERS 1968-1982

FILE SCISEARCH

FILE COVERS 1974 TO 14 Dec 2006 (20061214/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONFSCI

10/518,503

FILE COVERS 1973 TO 14 Nov 2006 (20061114/ED)

CSA has resumed updates, see NEWS FILE

FILE DISSABS

FILE COVERS 1861 TO 27 NOV 2006 (20061127/ED)

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FILE MARPAT

FILE CONTENT: 1961-PRESENT VOL 145 ISS 25 (20061215/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES (COVERAGE TO THESE DATES IS NOT COMPLETE):

US	20060247444	02 NOV 2006
DE	102005020105	26 OCT 2006
EP	1717297	02 NOV 2006
JP	2006302757	02 NOV 2006
WO	2006116773	02 NOV 2006
GB	2425654	01 NOV 2006
FR	2884821	27 OCT 2006
RU	2286328	27 OCT 2006
CA	2545188	28 OCT 2006

Expanded G-group definition display now available.

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